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APPLICATION OF DICOUMARIN (3,3'-METHYLENE-BIS-[4-HYDROXYCOUMARIN]) IN TRAUMA AND GANGRENE

CHARLES E BRAMBEL, PH D

AND

F FORD LOKER, MD
BALTIMORE

The problems of the control of intravascular disorders have been the subject of intensive investigation for many years. Recent developments in chemotherapy have produced an agent, dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) capable of inhibiting coagulation of blood *in vivo*. This compound exerts no anticoagulant properties on blood directly but produces its effect through some organic tissue of the body. A survey of the literature¹ reveals that some interesting and valuable clinical results have been obtained with this compound. From current investigations² evidence is accumulating that the coagulation of blood can be impaired without deleterious effects on the organism. It is our purpose to demonstrate that therapeutic impairment of the coagulation mechanism by chemical agents has proved decidedly advantageous in cases of trauma and of various types of gangrene. Vascular failure resulting in thrombosis and gangrene has been found to be controllable by *in vivo* anticoagulants. Such surgical applications of these chemical agents should prove of inestimable value during the present national emergency when industrial accidents, war wounds and other conditions incident to war, such as trench and immersion foot, are so prevalent.

Following trauma, whether surgical, accidental or incurred during battle, the coagulation property of the blood is enhanced and this is expressed in terms of increased activity of prothrombin³ and resistance to heparin⁴. This increased

From the Departments of Clinical Biochemistry and Surgery, Mercy Hospital

1 (a) Bingham, J B, Meyer, O O, and Howard, B. Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin). III. A Report on Further Clinical Observations, *Am J M Sc* **205** 587, 1943. (b) Bingham, J B, Meyer, O O, and Pohle, E J. Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin). I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, *ibid* **202** 563, 1941. (c) Bollman, J L, and Preston, F W. The Effects of Experimental Administration of Dicoumarin, *J A M A* **120** 1021 (Nov 28) 1942. (d) Butsch, W L, and Stewart, J D. Administration of Dicoumarin Compound for Prophylaxis of Postoperative Thrombosis and Embolism, *Arch Surg* **45** 551 (Oct) 1942. (e) Davidson, C S, and MacDonald, H. A Critical Study of the Action of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) (Dicoumarin), *Am J M Sc* **205** 24, 1943. (f) Meyer, O O, Bingham, J B, and Axelrod, V H. Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin). II. The Method of Administration and Dosage, *ibid* **204** 11, 1942. (g) Shapiro, S, Sherwin, B, and Gordimer, H. Postoperative Thrombo-Embolization, *Ann Surg* **116** 175, 1942. (h) Wright, L, and Prandoni, A. The Dicoumarin, 3,3'-Methylene-Bis-(4-Hydroxycoumarin). Its Pharmacologic and Therapeutic Action in Man, *J A M A* **120** 1015 (Nov 28) 1942.

2 Allen, E V, and Barker, N W. Vascular Clinics. XVII. A Conjecture Concerning Benefits to Man of Artificially Impaired Coagulation of the Blood, *Proc Staff Meet Mayo Clin* **18** 107, 1943.

3 Brambel, C E, and Loker, F F. Significance of Variations of Prothrombin Activity of Dilute Plasma, *Proc Soc Exper Biol & Med* **53** 218, 1943.

(Footnote continued on next page)

tions of prothrombin activity in undiluted plasma Brambel and Loker² found that 12.5 per cent plasma (diluted with isotonic solution of sodium chloride) was the most sensitive dilution with reference to indicating the degree of the tendency toward acceleration of plasma clotting in relation to deviation of persons from normal For undiluted normal human plasma a prothrombin clotting time of twelve to fifteen seconds was consistently obtained from the plasma of 75 healthy persons chosen at random, and a clotting time of ninety-five \pm ten seconds was obtained from plasma diluted eight times with isotonic solution of sodium chloride The prothrombin clotting time for dilute normal plasma obtained during the course of the present investigation deviates considerably from that reported by Quick and other investigators for the same dilution A value of forty seconds was reported by the majority of other investigators for this concentration of plasma¹¹ An explanation of this marked discrepancy is lacking at the present time since the directions described by Quick for the preparation of the reagents were followed in every detail However, the physicochemical characteristics of rabbit thromboplastin and its preparation may easily be responsible for the differences encountered, since our knowledge of the chemistry of this reagent is meager

Our routine procedure consisted of two determinations of the prothrombin clotting time—on undiluted oxalated plasma prepared according to the directions of Quick, and on plasma diluted eight times with isotonic solution of sodium chloride The method outlined has proved to be a biochemical means of evaluating the physiologic response of the organism to injury with respect to the coagulative properties of the blood Just at what point this physiologic response becomes a pathologic condition resulting in thrombophlebitis, etc., or what factors transform a natural process into a disease are unknown at present In all the cases in which thrombophlebitis developed this event was predictable from the data obtained on dilute plasma

The method of Lee and White¹² was used to determine the coagulation time of whole blood in connection with heparin studies

CLINICAL MATERIAL

The clinical material consisted of a series of cases involving various types of gangrene and trauma, classified as follows (a) post-traumatic condition with associated gangrene following crush injury, (b) diabetic and arteriosclerotic gangrene, (c) frostbite The efficacy of *in vivo* blood anticoagulants namely dicoumarin and heparin, was studied in these conditions Dicoumarin was used more extensively than heparin because of ease of administration

The principles involved in the following thesis have been used as a guide in all cases in which treatment was given during the course of this investigation In trauma and gangrene the following conditions are manifest

1 Conditions favoring thrombus formation

(a) Injury to the endothelial lining of blood vessels

(b) Accelerated prothrombin clotting time (detectable in dilute plasma)

(c) Liberation of excess thromboplastin (thrombokinas) by traumatized tissue¹⁴

2 Marked swelling which interferes with normal circulation and oxygenation of the tissues

12 Pohle, F J, and Stewart, J K A Study of the Quick Method for the Quantitative Determination of Prothrombin with Suggested Modifications, *Am J M Sc* **198** 622, 1939
Brigham and others^{1a b} Quick^{10a} Shapiro and others¹⁵ Shapiro and others¹¹

13 Lee, R L, and White, P D A Clinical Study of the Coagulation Time of Blood, *Am J M Sc* **145** 495, 1913

14 de Takats, G Thrombosis and Embolism, in Christopher, F Textbook of Surgery, ed 3, Philadelphia, W B Saunders Company, 1941 Jacob, F Thrombosis and Embolism After Closed Injuries of the Limbs, *Schweiz med Wchnschr* **73** 117, 1943, abstracted, *Internat S Digest* **36** 74, 1943 de Takats⁴

These conditions are conducive to thrombosis, and gangrene may ensue unless measures are taken to inhibit occlusion in the vessels of the extremity. By means of *in vivo* anticoagulants the enhanced prothrombin clotting mechanism can be disrupted for any desired period without deleterious effects in the patient. In this manner proper physiologic circulation can be maintained until natural processes supervene. All of the patients because of their enhanced coagulation mechanism exhibited definite resistance to the effects of dicoumarin when compared with normal persons. Larger doses of the hemorrhagic compound were necessary to produce the same effect, and the period of duration was shorter.

Heretofore, it was a matter of conjecture whether or not progressive gangrene would occur with consequent loss of an appendage. In the cases to be presented, it was predicated that the loss of the extremity was highly probable, but in no instance was it necessary to perform a major amputation following a crush injury.

POST-TRAUMATIC CONDITIONS

Experience has shown that gangrene may readily develop in extremities four to seven days after trauma that has resulted in lacerations and severe crushing injuries. It is well established that in extremities that have been caught in heavy machinery gangrene may develop in spite of the fact that they appear viable as long as seventy-two hours after the trauma. However, postoperative amputation was unnecessary in any of the 6 cases presented in this group. To date, 10 cases of crush injuries to extremities have been studied, with satisfactory results. No bleeding occurred as the result of the administration of the hemorrhagic compound. For four of the patients amputation of fingers appeared imminent on admission. However, the extremities were repaired surgically and therapy with dicoumarin was started immediately. The subsequent course of recovery was uneventful, and healing by first intention occurred.

Course of Treatment—Each patient was first treated in the accident room, where the injured extremity was cleansed with soap and water, ether and solution of merthiolate. Following admission, the patient was removed to the operating room and surgical repair carried out as indicated. In 2 cases the administration of heparin was begun by intravenous drip before recovery from anesthesia. A coagulation time of fifteen minutes was maintained for the venous blood for twenty-four hours. Dicoumarin was administered orally as soon as the patient was able to swallow. The prothrombin clotting time was determined on alternate days throughout the course in the hospital. The administration of dicoumarin was continued in 300 mg doses until the prothrombin clotting time ranged between thirty and thirty-five seconds for undiluted plasma. An effort was made to maintain this level of decreased prothrombin activity, controlled by frequent determinations of plasma clotting time. In this manner, overdosage of the hemorrhagic principle was avoided as well as any consequent deleterious effects, such as purpura and hemorrhage. The response was found to be extremely variable but reasonably predictable for any single patient after the coagulation was disrupted.

CASE 1 *Crushing injury of the left foot with deep pressure lacerations and beginning gangrene*—A 52 year old white man was admitted to Mercy Hospital on April 19, 1943. The previous day a large moving truck ran over his left foot. Roentgen examination of the injured foot revealed a linear fracture of the cuboid bone without displacement and fractures of the distal ends of the second phalanges of the second, third, fourth and fifth toes. There was a displacement of the distal fragment of the fourth toe, otherwise the alignment was good. A deep pressure laceration was aseptically cleaned, sulfanilamide powder was placed in the wound, the edges were approximated with silk and antitetanus serum was given.

The familial and the past history were without special bearing on the case except for an episode of typhoid several years prior to admission. Physical examination showed no abnormality except for the left foot, which was markedly swollen and ecchymotic. The third toe on the left foot was markedly cyanotic and felt colder than the remaining toes. The distal phalanx suggested beginning gangrene. Long lacerations were present on the dorsum of the foot, running parallel to the long axis of the foot and extending from about the tarsal region to the base of the toes.

The patient was given the usual care of rest in bed and elevation of the leg, and a heating cradle was placed over the extremities. Dicoumarin therapy was begun on April 20. See table 1 for the dosage and the response. On April 22 the foot was dressed. The distal phalanx of the third toe was black and endaveous in appearance. Marked vesiculation appeared over the dorsum of the foot proximal to the bases of the toes. The dorsalis pedis artery was palpable. On April 24 the foot was redressed. The edges of the wound did not appear healthy, serous ooze was noted between the sutures, and several sutures were removed to allow drainage. The third toe was unclamped, while the second toe was cold and the color not good. It was felt that unless the clotting mechanism could be rapidly altered the foot distal to the site of trauma would become gangrenous. The response to dicoumarin was poor (table 1). Large doses of dicoumarin were then administered with satisfactory disruption of the clotting mechanism. The appearance of the foot gradually improved, the color of the second toe assumed a normal tint, and the edges of the wound regained their healthy appearance. The blisters on the dorsum of the foot disappeared, the epidermis desquamated leaving a healthy normal skin beneath and the swelling subsided. The distal phalanx of the third toe was definitely gangrenous, but the process did not extend beyond this point. On May 17, with the patient under anesthesia induced with pentothal sodium the distal phalanx of the third toe was removed and the skin closed over the stump. Uneventful recovery ensued. The patient was discharged May 29 as completely recovered.

Comment. Undue caution was used in the administration of dicoumarin. After several days it was possible to maintain a constant clotting time of between twenty-five and thirty seconds for undiluted plasma until the danger of progressive gangrene appeared to be passed, at which time the level was purposely lowered. Subsequent similar cases have proved that the patient's blood was kept at a prolonged clotting time for a period longer than necessary. Too long a period elapsed between the date of injury and the appropriate prolongation of the prothrombin clotting time. Heparin was definitely indicated for this patient. He gave all evidence of an imminent gangrene of the distal part of the foot, which was apparently prevented by the use of dicoumarin.

CASE 2. *Crushing injury of the left hand and partial amputation of the left index finger.*—A 28 year old white man was admitted to Mercy Hospital on June 21, 1943 with the complaint of having caught his hand in a mechanical roller. The injury resulted in incomplete amputation of the left index finger and multiple deep pressure lacerations on the dorsum of the hand, index and middle finger. Antitetanus serum was given and the patient taken to the operating room. With the patient under general anesthesia, the hand was surgically cleansed. The index finger was sutured back in place, and the remainder of the repair of the hand was accomplished.

The familial and the past history and the review of systems gave essentially negative information. Physical examination gave negative results except for the injury to the hand.

Heparin was administered by intravenous drip before the patient recovered from the anesthetic. One liter of 0.9 per cent saline solution and 200 mg. of heparin was used and required eighteen hours for administration at the rate of 20 to 24 drops per minute. During this period the coagulation time of the whole blood was maintained at fifteen minutes. Dicoumarin (300 mg.) was given orally as soon as the patient was able to swallow.

Although the main arterial supply of the index finger was not severed, the distal portion felt cold and appeared dusky. Two days postoperatively, the hand was dressed, and all the digits appeared viable. Normal warmth had returned to the severely damaged index finger. The patient was discharged on the seventh postoperative day.

Comment. Under ordinary circumstances the index finger would have been amputated at operation, but in view of the interest in heparin and dicoumarin therapy in such injuries, the operator decided to repair the partially amputated finger. At this time it appeared that the index finger would not remain viable. After appropriate therapy, the expected result was obtained, namely, no digits were lost through amputation. Follow-up three weeks and five weeks later revealed uneventful improvement. This case clearly illustrates the efficacy of combined dicoumarin and heparin therapy in severe crush injuries.

CASE 3 Crushing injury of the left hand with severe deep pressure lacerations—A 19 year old white man was admitted to Mercy Hospital on June 4, 1943. Train wheels had crushed the patient's left hand. All four fingers were split open from the tips of the fingers down to the bases. The middle finger appeared worse than the others, and the bones were crushed to a degree which made repair impossible. The middle finger was taken off down to the proximal phalanx. The ruptured palmar surface of the proximal phalanx was closed. The index and ring fingers were amputated at the junction of the middle and distal phalanges, and the ruptured palmar surfaces were sutured. Five grams of sulfanilamide was sprinkled over the fingers.

The family history, the past history and the physical examination were noncontributory.

Heparin was administered by interrupted intravenous doses, and a coagulation time of fifteen minutes was maintained for twelve hours. Dicoumarin was given orally in two doses (table 1). The patient was discharged on the fifth postoperative day as improved. Subsequent follow-up revealed healing of the crushed hand by first intention.

Comment No subsequent amputations were necessary in this patient with a severe crush injury. The dicoumarin therapy was of short duration and appeared to be adequate. The impression obtained from this case was that the patient would have lost all four fingers back to the midpalm region if *in vivo* anticoagulants had not been used.

CASE 4 Crushing injury of the right hand with complete amputation of the index, middle and ring fingers at the metacarpal phalangeal joint—A white man aged 17 was admitted to Mercy Hospital on July 28, 1943 through the accident room after having caught his right hand in a stamping press, the index, middle and ring fingers had been completely amputated at the metacarpal phalangeal joint. The patient was taken to the operating room, and a plastic operation was done on the stump.

A review of systems and physical examination gave essentially negative results except for the aforementioned injury.

At operation it was noted that the thumb and the little finger were the only digits remaining on the hand. In order to make a viable stump, it was necessary to resect the metacarpal bones about two thirds of their length. This gave a fair stump, but the edges of the skin when sutured together were under more tension than was desirable. To cut back farther would have destroyed what little function the fifth finger might have and would have destroyed its blood supply completely. It was deemed advisable to accept the skin flap under tension and use dicoumarin with the hope that the tight flaps would remain viable. The hand was dressed on the second postoperative day, and there was no evidence of sloughing. However, the little finger was cold, and its color was not healthy. By the fourth postoperative day the color in the little finger had improved. There was slight vesiculation at the base of this finger, on the dorsum, and several small vesicles were noted just proximal to the stump on the dorsum of the hand. In the region of the third and fourth metacarpal bones the edges of the skin sloughed at the line of stitches. There was no further evidence of gangrene. The patient was discharged on the tenth postoperative day with a viable stump. No further progress in the gangrene of the edges of the skin was noted.

Comment In this case the fingers were completely amputated by the accident, and to make a satisfactory stump having skin without any tension would have necessitated removal of the little finger and of all of the second, third and fourth metacarpal bones. Slight dissolution of tissue was noted along the part of the line of stitches where the tension of skin was most marked. After the stitches were removed in this area there was no extension of the gangrene. In spite of the fact that it appeared at first that the little finger would not remain viable, the end result gave a normally functioning digit. It was felt that a larger portion of the traumatized member would have been sacrificed if dicoumarin therapy had not been used. A number of similar cases have been observed in which in the absence of *in vivo* anticoagulants the flaps became gangrenous and sloughed, necessitating a long period of hospitalization to allow healing by granulation and skin grafting.

TABLE 1—*Dosage and Response in Cases 1 to 11*

Hospital Days	Case 1			Case 2			Case 3			Case 4			Case 5			Case 6			Case 7			Case 8			Case 9			Case 10			Case 11		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C			
1	13	78	300				17	70	300				17	70	300	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
2																0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
3																0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
4	14	67	300	15	130	300	17	70	300	17	70	300	24	180	300	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
5																0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
6	17	130	300				40	400		40	400		172	400		2	100		0	0		0	0	0	0	0	0	0	0	0			
7	25	170											100	400		0	0		0	0		0	0	0	0	0	0	0	0	0			
8	25	300	300	17	170		0	124	700	0	124	700	92	400		10	100		0	0		0	0	0	0	0	0	0	0	0			
9	22	220											Discharged			0	100		0	0		0	0	0	0	0	0	0	0	0			
10	22	300	300				27	220	300				Discharged			0	100		0	0		0	0	0	0	0	0	0	0	0			
11	25	210														0	100		0	0		0	0	0	0	0	0	0	0	0			
12	13	130	00													0	100		0	0		0	0	0	0	0	0	0	0	0			
13	20	170														0	100		0	0		0	0	0	0	0	0	0	0	0			
14	17	125	300													0	100		0	0		0	0	0	0	0	0	0	0	0			
15	20	150	300													0	100		0	0		0	0	0	0	0	0	0	0	0			
16	21	300														0	100		0	0		0	0	0	0	0	0	0	0	0			
17	27	175	300													0	100		0	0		0	0	0	0	0	0	0	0	0			
18	24	300														0	100		0	0		0	0	0	0	0	0	0	0	0			
19	20	150	300													0	100		0	0		0	0	0	0	0	0	0	0	0			
20	20	212														0	100		0	0		0	0	0	0	0	0	0	0	0			
21	20	220	300													0	100		0	0		0	0	0	0	0	0	0	0	0			
22	20	192	300													0	100		0	0		0	0	0	0	0	0	0	0	0			
23	22	171														0	100		0	0		0	0	0	0	0	0	0	0	0			
24	27	300														0	100		0	0		0	0	0	0	0	0	0	0	0			
25	25	205														0	100		0	0		0	0	0	0	0	0	0	0	0			
26	20	150														0	100		0	0		0	0	0	0	0	0	0	0	0			
27	12	80														0	100		0	0		0	0	0	0	0	0	0	0	0			
28																0	100		0	0		0	0	0	0	0	0	0	0	0			
29																0	100		0	0		0	0	0	0	0	0	0	0	0			
30																0	100		0	0		0	0	0	0	0	0	0	0	0			
31																0	100		0	0		0	0	0	0	0	0	0	0	0			
32																0	100		0	0		0	0	0	0	0	0	0	0	0			
33	12	63														0	100		0	0		0	0	0	0	0	0	0	0	0			
34																0	100		0	0		0	0	0	0	0	0	0	0	0			
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38																0	100		0	0		0	0	0	0	0	0	0	0	0			
39																0	100		0	0		0	0	0	0	0	0	0	0	0			
40																0	100		0	0		0	0	0	0	0	0	0	0	0			

Discharged

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24 260 200

Discharged

19 122 300

35 400

29 270

17 97

Discharged

Discharged

Discharged

Discharged

A—Undiluted plasma prothrombin clotting time in seconds
B—Dilute (1:5 per cent) plasma prothrombin clotting time in seconds
(—VIII) runs of dicoumarin administered orally

TABLE 2—Summary of Data on Cases 1 to 11

Case	Hospital No	Description	Age, Yr	Sex	Race	Days in Hospital	Total Dose of Dicoumarin Mg	Total Dose of Heparin Mg	Bleeding	Sulfonamide Compound Given Orally	Reamputations	Result
1	56739	Crush injury of foot, beginning gangrene of toe	52	M	White	42	3,100				None	Improved
2	57784	Crush injury of hand, lacerations, no gangrene	28	M	White	5	600	100			None	Improved
3	54487	Crush injury of hand, no gangrene	19	M	White	5	700	200			None	Improved
4	58442	Crush injury of hand complete amputation of fingers, no gangrene	17	M	White	11	1,100				None	Improved
5	58295	Incomplete amputation of finger, no gangrene	74	M	White	7	800				None	Improved
6	57725	Crush injury of hand incomplete amputation, no gangrene	32	M	Negro	9	1,000	200			None	Improved
7	57723	Diabetic gangrene of foot	63	F	White	82	1,800			Sulfathiazole	None	Improved
8	57829	Diabetic gangrene of foot	49	F	White	67	1,000			Sulfathiazole	None	Improved
9	58425	Diabetic gangrene of foot	54	M	White		2,500			Sulfathiazole	None	Improved
10	56167	Arteriosclerotic gangrene of foot	63	M	Negro	67	900			Sulfathiazole	None	Improved
11	57918	Frostbite beginning, gangrene of toes	11	M	Negro	11	50		Ulcerated areas	Sulfathiazole	None	Improved

CASE 5 *Severe lacerations and compound fracture of the left middle finger*—A 74 year old white man was admitted to Mercy Hospital through the accident room Aug 4, 1943. He had received such a severe injury to his left middle finger that only the palmar integument was intact. The finger was sutured back in place and a splint applied.

The family history, the past history and the physical examination gave negative information except for the aforementioned injury.

The course of this patient in the hospital was uneventful except for one attack of nausea following the ingestion of dicoumarin. At this time it was thought that the hemorrhagic compound was lost, and another dose was administered the following day. However, a marked increase in the prothrombin clotting occurred (table 1). No bleeding from the wound took place. The patient was discharged on the seventh hospital day as improved.

Comment This patient had an injury that would obviously have involved an amputation on admission. Through the use of an *in vivo* anticoagulant, dicoumarin, normal physiologic circulation was obtained, and the injured finger remained viable. In addition, the case demonstrates the possibility of disrupting the coagulation mechanism to an extreme limit without hemorrhagic sequelae, *i. e.*, hematuria, purpura, etc.

CASE 6 *Crushing injury of the left hand with amputation of the distal phalanx of the index finger in an accident*—A 32 year old Negro man was admitted to the accident room of Mercy Hospital on June 19, 1943 after having suffered a severe crushing injury to his left hand involving four fingers and the carpal and metacarpal regions of the hand. The injury was sustained while the man was riding on a truck which overturned, his hand was caught between the pavement and the truck. The distal phalanx of the index finger was completely amputated by the accident. The remaining fingers were severely crushed. There was a compound fracture of the middle phalanx of the ring finger. The patient was taken to the operating room for the purpose of amputating the third, fourth and fifth fingers. However, dicoumarin and heparin therapy was considered, and the macerated digits were repaired.

The family history, the previous history and the physical examination gave entirely negative information except for the aforementioned conditions.

The patient made an uneventful recovery except for a slight secondary infection which appeared on the fifth finger on July 1. Continuous warm boric acid compresses were begun, and by July 4 the infection was completely cleared up. The patient was discharged on the following day as recovered.

Comment Combined heparin and dicoumarin therapy was used in this case, and the anticipated results were obtained. There was no evidence of gangrene in any of the fingers. There is no way of proving, however, that the blood supply in these fingers would not have been maintained even if dicoumarin had not been administered. Judging from similar cases seen prior to the availability of oral *in vivo* anticoagulants, we feel that the hemorrhagic principle dicoumarin was of definite value in maintaining the viability of the injured fingers.

DIABETIC AND ARTERIOSCLEROTIC GANGRENE

Dicoumarin was administered to 3 patients for diabetic gangrene and to 1 patient for arteriosclerotic gangrene uncomplicated by diabetes, but associated with marked uremia. Two of the patients had a minimal amount of infection with marked arteriosclerosis (cases 7 and 8). One patient had a minimum of arteriosclerosis and a maximum of infection (case 8). The case of arteriosclerotic gangrene complicated by uremia (case 10) graphically demonstrated the effect of poor renal function on the physiologic action of dicoumarin. Administration of the *in vivo* anticoagulant had to be discontinued because of the prolonged duration of the hemorrhagic effect from a single small dose.

Chemotherapy was used with the hemorrhagic compound on the basis of the thesis outlined on an earlier page. In every case in the group a marked increase in prothrombin activity of dilute plasma was manifested. In these cases an effort

was made to maintain the inhibition of the coagulation mechanism during the inflammatory period. However, it is realized that other factors, such as infection and level of blood sugar, play a major role in aggravating the gangrenous condition. Other therapeutic agents, i. e., sulfathiazole and sulfadiazine, were used in conjunction with dicoumarin. Thus, two chemotherapeutic agents were used concomitantly, one to check the harmful effects of invading organisms and the other to inhibit the coagulation mechanism of the blood and prevent thrombosis of peripheral vessels in the erythematous area. No antagonism between the two diverse chemical agents was observed as long as a good intake and output of fluids was maintained. Furthermore, no toxic effects were apparent from the dosages used.

Course of Treatment—Dicoumarin was administered orally immediately after the patient's admission to the hospital. The appropriate sulfonamide compound was used simultaneously to combat infection. An effort was made to maintain the prothrombin clotting time of thirty-five to forty-five seconds for undiluted plasma which has been found by us to be the optimum therapeutic level. Some deviations were encountered, but no bleeding from ulcerated areas took place. When the level of prothrombin activity was lower than desired, the administration of dicoumarin was stopped. Within twenty-four to thirty-six hours after cessation of dosage, an increase in coagulation activity was noted, and the administration of the hemorrhagic compound was resumed as indicated.

CASE 7 Diabetic gangrene of the left foot—A 66 year old white woman was admitted to Mercy Hospital on June 17, 1943 with an abscess of the left foot and beginning gangrene. Two weeks prior to admission she had run a nail into her foot. Although she was known to be diabetic, she had not been following her diet or using insulin.

Physical examination showed a normal person except for the findings mentioned with regard to her foot. The left foot was swollen and edematous, with a puncture wound on the plantar surface showing definite abscess formation. The second and third toe manifested signs of beginning gangrene.

The abscess was incised and drained on June 17. Oral administration of sulfathiazole was started on June 19 and was continued to July 7 (1 Gm every four hours). Sodium tetrathionate was given intravenously in daily doses from June 20 to July 15. Administration of dicoumarin was started on June 17 and continued throughout the course in the hospital. The diabetic condition was controlled by insulin and diet. On August 3 the patient's left leg was amputated below the knee. During the period in the hospital, tests for hepatic function were carried out, and no evidence of impairment was revealed.

The patient was discharged as improved September 7.

Comment Dicoumarin, sulfathiazole and sodium tetrathionate, as well as the usual medications, were given concomitantly without untoward reactions in this patient. From these findings it might be concluded that there are no contraindications for the use of dicoumarin in conjunction with the administration of sulfonamide compounds. Furthermore, this case demonstrates the fact that the hemorrhagic compound dicoumarin can be tolerated by patients for long periods without apparent toxic manifestations.

On consultation, a mid thigh amputation was recommended. However, amputation below the knee was performed with satisfactory results, suggesting that the therapeutic principles formulated elsewhere in this paper yielded a predicted course.

CASE 8 Early diabetic gangrene of the fourth and fifth toes of the left foot in a patient with minimal arteriosclerosis—This patient was a 48 year old white woman, admitted to Mercy Hospital on June 25, 1943 with the complaint of infection of the left foot. She stated that the infection started two weeks prior to admission after the trimming of a corn on the fourth toe. The toe became progressively worse and began to change from a red to a purplish color. The third and fifth toes also showed signs of becoming involved.

The family history was noncontributory, the previous history was relative only in that the patient had had diabetes mellitus for eight years. Evidence of beginning gangrene was present on the fourth and fifth toes of the left foot, extending for about 2 Cm on the plantar and dorsal surfaces. Pus was seen exuding between the third and fourth toes. A fluctuant

swelling was observed on the dorsum of the foot extending to the third and fourth toes. The dorsalis pedis arteries were easily palpable in both feet.

The patient was put at rest in bed. Incision and drainage were carried out, with the patient under anesthesia induced with pentothal sodium and administration of sulfathiazole and dicoumarin was begun. The foot was elevated and a heating cradle placed over the bed. The infection gradually cleared up, and frequent dry dressings were applied. On admission the blood sugar amounted to 217 mg per hundred cubic centimeters. Roentgen study of the foot revealed destruction of the greater portion of the bone of the first phalanx of the fourth toe. During the subsequent weeks the flexor tendon of the fourth toe and part of the plantar fascia sloughed out.

After several weeks, warm boric acid soaks were started and administered three times a day. Improvement continued, amputation was unnecessary, and normal color and sensation returned to the involved toes. The patient was discharged on August 31, with almost complete healing.

Subsequent follow-up in the outpatient department revealed that the foot was completely healed except for a small area on the dorsum at the metatarsal phalangeal junction of the fourth toe.

Comment This patient had beginning gangrene of the third, fourth and fifth toes. Indications were present which predicated the loss of the fourth and fifth toes even with the aid of the *in vivo* anticoagulant. We feel that dicoumarin was a potent factor in the recovery of this patient without the loss of any toes or even of the entire leg. Conversely, the fact cannot be minimized that the patient had little or no arteriosclerotic changes, as indicated by palpable dorsalis pedis arteries in both feet.

CASE 9 *Early diabetic gangrene of the second, third and fourth toes of the right foot*—A 54 year old white man was admitted to Mercy Hospital on July 28, 1943 with the complaint of an infected area on the plantar surface at the base of the third toe and marked discoloration of the great toe and of the second, third and fourth toes. The usual area of erythema and brownish induration preceding gangrene of the toes extended to the region of the ankle. The dorsalis pedis artery was not palpable.

The family history and the past history were noncontributory.

Physical examination gave essentially normal results except for the beginning gangrene of the second and third toes.

The patient was put at rest in bed, and a heating cradle was placed over the feet. The temperature was 103 F on admission, and the blood sugar level was found to be 222 mg per hundred cubic centimeters. Oral administration of dicoumarin and sulfathiazole was begun.

Immediate improvement was not observed. The gangrene progressed, involving the entire third toe and about 2 cm along the dorsum of the foot. For several days the appearance of the foot indicated that the great toe and the third toe would be lost since they became cyanotic and cold. Furthermore, marked difficulty was experienced in controlling the diabetic condition, and it was found that the patient was accepting additional food brought to him by his family and friends.

After seven to eight days improvement was noted in the foot. The erythematous area began to recede, the first, second and fourth toes began to regain their normal color. About three weeks after admission the third toe was removed without anesthesia, and there was no further extension of the gangrenous process. At the time of writing the patient is still confined to the hospital. However, the reparative processes have reached a point which suggests uneventful recovery and discharge from the hospital in the near future. This patient will be followed in the outpatient department at the time of further dressings.

Comment This patient has been a problem throughout his stay in the hospital. He has repeatedly broken his diet and during his period of convalescence has been walking on his affected foot against the advice of the attendants. We feel that even less tissue might have been lost had it been possible to control the diabetic condition more effectively. This patient was a potential candidate for a mid thigh amputation. Dicoumarin therapy was effective in maintaining physiologic circulation in the affected member and undoubtedly inhibited the gangrenous process.

CASE 10 *Arteriosclerotic gangrene of the right foot with infection*—A 68 year old Negro man was admitted to Mercy Hospital on March 9, 1943 because of gangrene involv-

conditions favoring thrombus formation. It is realized, however, that much additional information is necessary to support the principles outlined.

The use of *in vivo* anticoagulants (dicoumarin) in the treatment of patients with granulating and ulcerative lesions is not contraindicated if caution and adequate control are exercised. In this connection, too much emphasis cannot be placed on the value of frequent determinations of the prothrombin clotting time as an index to dosage. No set dosage for dicoumarin was found for the patients in the series of cases presented. In some the clotting mechanism was found to be refractive, and therefore they required much larger doses than others.

No contraindications were found when sulfonamide compounds and the hemorrhagic agent (dicoumarin) were used concomitantly if average normal renal and hepatic function were present. Table 2 presents a summary of the total doses of dicoumarin and sulfonamide compounds used. No evidence of hepatic damage following long periods of oral administration of the hemorrhagic compound was demonstrable by any available test.^{10a}

One patient (case 10) was treated by amputation below the knee since it was feared that he could not withstand the shock of midthigh amputation. This one instance suggests that the time-honored procedure of midthigh amputation in a patient with arteriosclerotic and diabetic gangrene of the toes may be supplanted by amputation at a site of election below the knee if dicoumarin is administered. This thesis was supported in another patient (case 7) whose leg was amputated below the knee for diabetic gangrene of the toes.

Colonel Walter Wise and Dr. Henry T. Collenberg gave advice and Miss Elizabeth J. Curtis technical assistance throughout this investigation.

The dicoumarin used in this investigation was supplied by the Abbott Laboratories of Chicago.

Roche-Organon Inc., Nutley, N. J., furnished the heparin preparation used (liquemmin).

TOXICOPATHOLOGIC STUDIES ON THE DYE T-1824

W C HUEPER, M D

AND

C T ICHNIOWSKI, P H D
NEW YORK

Evans blue or dye T-1824 is an azo dye produced by an interaction of o-tolidine with Chicago acid (1-amino-8-naphthol-2,4-disulfonic acid) and has a molecular weight of 960 (Gregersen and Rawson,¹ Rawson²) It has been used for a number of years by numerous workers for the determination of total plasma volume in man and experimental animals³ and has been tried in the treatment of experimental cancer⁴ In spite of the relatively extensive administration of this dye, almost nothing is known concerning its toxic properties

The experiments to be reported were undertaken for the purpose of providing at least some fundamental data on this aspect

EXPERIMENTAL PROCEDURE AND OBSERVATIONS

The dye used was synthesized by Dr C Lischer, of the Warner Institute for Therapeutic Research, and was purified so as to conform with the standards established for this dye by Gregersen, according to spectroscopic methods In accordance with the purpose of the experiment, a sterile 0.5 per cent aqueous solution of T-1824 was injected intravenously into dogs, cats, rabbits and rats for the determination of an approximate single lethal dose and the symptomatic and anatomic toxic manifestations

Intravenous Injection of Dye T-1824 into Dogs—Six dogs weighing from 8.15 to 10.9 Kg received into the jugular vein one injection of the 0.5 per cent dye solution One dog (1) was given 1 cc per kilogram, 2 dogs (2 and 3) 3 cc, 1 dog (4) 5 cc, 1 dog (5) 10 cc and 1 dog (6) 25 cc Dog 6 died seventeen hours later, after an attack of vomiting and diarrhea with expulsion of bluish-colored material shortly after the administration of the dye Dog 5 died five weeks and dog 3 died approximately seven weeks after the injection The other 3 dogs of the series survived and were put to death by an intravenous injection of a 4 per

From the Warner Institute for Therapeutic Research

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cent formaldehyde solution almost six months after the treatment. During this period no consistent effect on the weight curve was apparent. After the injection of doses of 3 cc and 5 cc per kilogram the dye was eliminated with the urine for at least seven days, and after the administration of 10 cc per kilogram for more than twelve days, according to the visible staining of the urine.

The autopsy of dogs 1, 2 and 4 resulted in the following observations. No abnormal conditions were present in dog 1, which received the smallest dose of the dye. In dogs 2 and 4 a bluish discoloration was found in the testes, the inguinal lymph nodes, the connective tissue of the prostatic gland and neck of the bladder, the adrenals, the intestinal wall, the renal cortex, the adventitia of the aorta, the pituitary gland and the lungs. In the lungs the bluish color appeared in the form of a fine stippling. The other organs were grossly normal.

The postmortem examination of dogs 3 and 5, which died five and seven weeks, respectively, after the injection, revealed lungs with large dark red hemorrhagic and grayish indurated pneumonic areas. In dog 3 a hemorrhagic exudate was present in the pleural and peritoneal cavities and a fibrinopurulent exudate in the pericardial cavity. The endocardium was discolored bluish, as were the adventitia of the aorta, the liver, the spleen, the renal cortex, the adrenal glands, the intestine and the testes. The brain was not discolored, while the meninges showed a slight bluish tinge. The testes were small. The autopsy of dog 6 showed greenish blue staining of thoracic and abdominal organs. There was an intensely blue fluid in the abdominal cavity, and some bluish liquid in the stomach. The gray substance of the brain had a bluish tint, while the white matter was unstained. The meningeal membranes were blue.

Histologic studies were made of the organs of dogs 2, 3, 4 and 5. The organs of dogs 2 and 4 were in general normal with the exception of the liver and the kidneys, which revealed degenerative parenchymatous lesions. The testes of both dogs showed some partially collapsed and degenerated seminiferous tubules. The retroperitoneal lymph nodes of dog 4 exhibited a broad fibrohyaline network, in the meshes of which large round cells loaded with a brown pigment were found. The aorta of this dog revealed a definite mucoid imbibition of the inner media, covered by small, circumscribed hyaline intimal cushions, and a larger area of hyalinization in the outer media.

In dog 3, which received 3 cc per kilogram, the lung showed hemorrhagic edema and the aorta considerable subintimal edema of the media and small hyaline foci between atrophic muscle cells beneath the endothelium (fig 1A). There was complete arrest of spermatogenesis in the testes, associated with some collapsed, atrophic tubules and tubules containing a few spermatid giant cells among the desquamated epithelial cells. In dog 5 large pneumonic and hemorrhagic areas were found in the lung. The leukocytes were mainly of the large mononuclear type. The aorta revealed a small hyaline intimal cushion (fig 1B). Large amounts of brown pigment were present in the phagocytes of the spleen and the lymph nodes. The spermatogenic tubules of the testes were completely atrophic and usually collapsed. They were lined in general only by Sertoli's cells and a few spermatogonia. The basement membrane was a thick hyaline band. The other organs (brain, hypophysis, heart, adrenal gland, liver, intestine, pancreas, lymph nodes, kidneys) were essentially normal with the exception of mild degenerative changes in the renal tubules.

Intravenous Injection of Dye T-1824 into Cats—Twenty-one cats were used in the experiment, 9 of which were studied histologically. Three cats received into the femoral vein 1 cc per kilogram of a 0.5 per cent solution of T-1824, 6 cats 3 cc, 4 cats 5 cc, 4 cats 10 cc and 4 cats 20 to 40 cc. The cats which received 10 cc or more per kilogram vomited soon after the injection, sometimes repeatedly with the higher doses, and had diarrhea. The dye was excreted visibly in the urine and feces for two to four days. The mortality rates and survival times are illustrated in table 1.

The table shows clearly that the mortality rate depends directly on the dose, being 100 per cent in the series receiving 10 cc or more per kilogram. A similar relation may be noted in regard to the length of survival of the animals that died from the effects of the dye injected, as all animals subjected to the high doses died either within a few hours (3 within two hours) or within periods up to fourteen days, while in the majority of the animals given the low doses that died death was much delayed.

The cats which died within two hours after the injection of the dye solution showed a blue discoloration of the entire organism including the skin, the subcutaneous tissue, the oral mucous membranes, the gastrointestinal tract, the liver, the spleen, the lymph nodes, the pancreas, the adrenal glands, the kidneys, the bladder, the heart, the periaortic connective tissue, the meninges, the lungs and the gray matter of the brain, the white matter of the brain was unstained. The blood serum and the saliva were also blue. There was no dye in the bile or the urine.

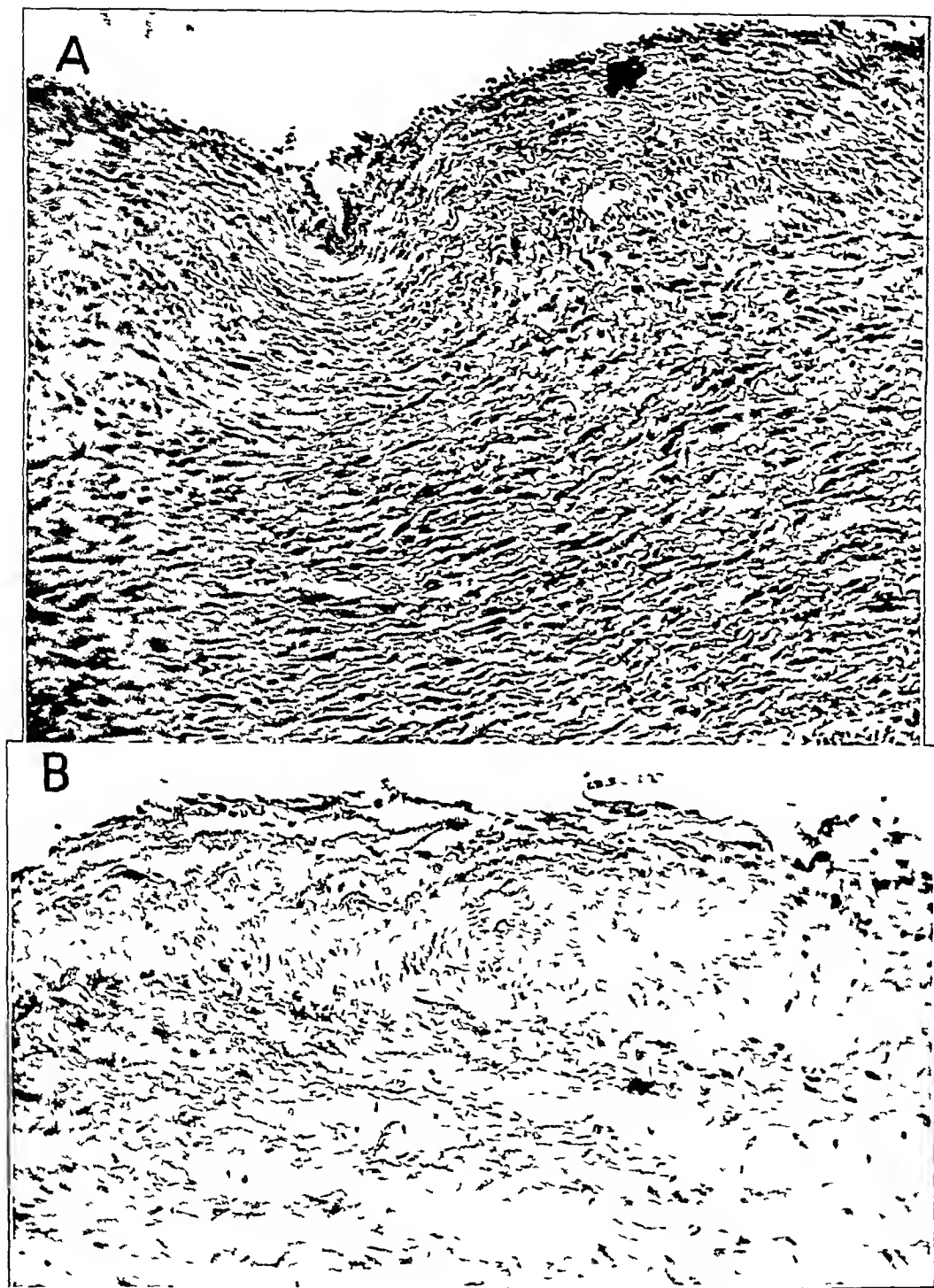


Fig 1—4, subendothelial hyaline thickening and necrosis of the aorta *B* cushion like, hyaline intimal thickening of the aorta

Similar observations were made on the animals which died within two to fourteen days. The internal organs had still a distinctly blue color. The gray matter of the brain was blue in some animals, in others it was unstained, whereas in a third group a bluish tracing corresponding to the cerebral vascular network was visible. The choroid plexus was blue. The thymus, the uterus and the ovaries, as well as the cartilage of the ribs, were deep blue. The lungs of several animals were edematous. There was a hemorrhagic exudate in the pleural cavities of 2 animals. One of these had also a greenish ascitic fluid. Another animal had extensive subepicardial hemorrhages involving especially the apex and the region of the left ventricle.

In the third group, with delayed death (six to ten weeks), the skin, particularly that of the ears, and the visible mucous membranes were still distinctly blue, as were most of the

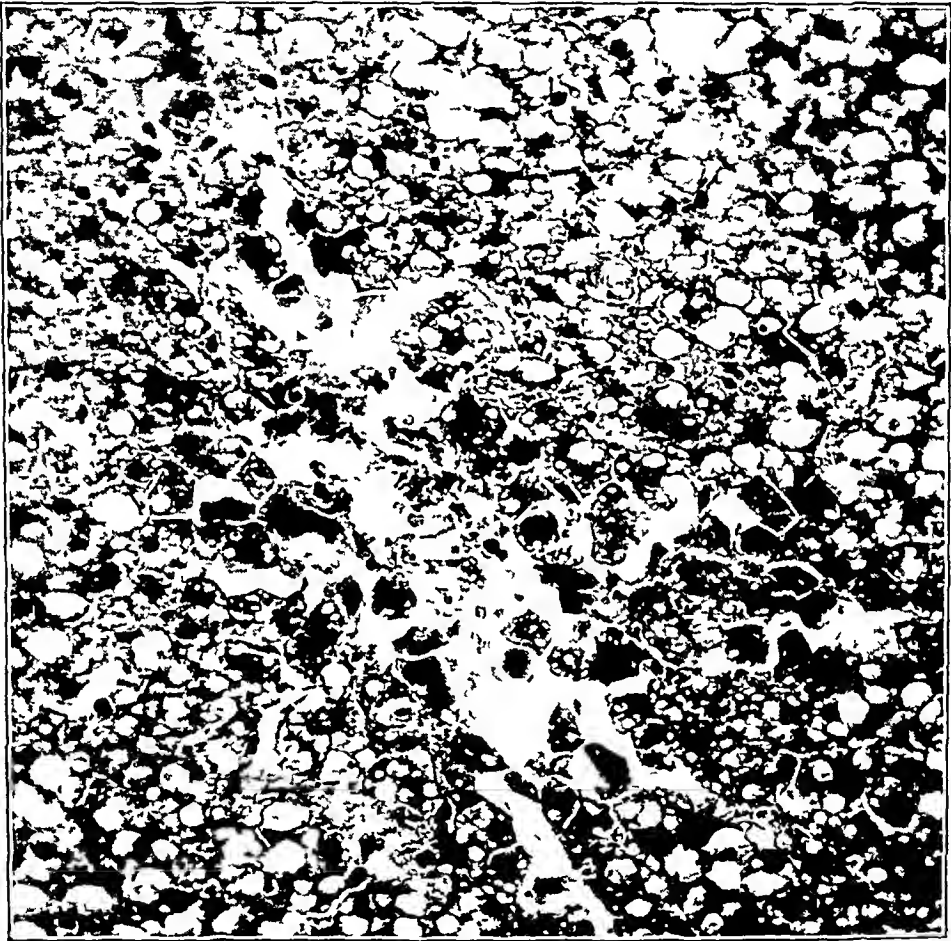


Fig 2—Marked vacuolar degeneration and dissociation of the liver cells

TABLE 1—Death and Survival Rates of Cats Given an Intravenous Injection of T-1824 Solution

Dose per kilogram	1 cc	3 cc	5 cc	10 cc	20 40 cc
1 Death in 1 to 24 hours	0	0	0	25%	50%
2 Death in 1 to 2 weeks	0	0	25%	75%	50%
3 Death in 6 to 10 weeks	33%	50%	25%	0	0
4 Survival	66%	50%	50%	0	0
Total number of animals	3	6	4	4	4

internal organs. The lung of one cat was edematous and hemorrhagic and that of a second was collapsed and brownish. Hemopericardium and hemorrhages into the ventricular wall were observed in one of these cats, while in a second fibrinous pericarditis was found.

Of the 5 cats which were killed six months after the injection, 3 revealed no traces of the dye, 1 showed a greenish cast to the liver, while in the fifth cat the pituitary gland, the ovaries and the periaortic fat tissues were still distinctly blue, and the liver, the renal cortex, the gastrointestinal tract and the adrenal glands had a greenish cast. The ears were green-blue, and the claws were greenish at the base.

The histologic examination of the organs of 4 cats which died one to ten weeks after the injection of the dye showed in all instances moderate to severe damage of liver cells ranging from severe edema and congestion to marked vacuolation with partial disintegration and complete absence of nuclei (fig 2). The tubular epithelium of the kidney was highly vacuolated. Hemorrhages and small necroses or abscesses were present in the myocardium of 2 cats. The brain showed a loss of nuclei in large ganglion cells and lysis of the Nissl substance in centers of the medulla oblongata. The other organs were essentially normal. Similar but

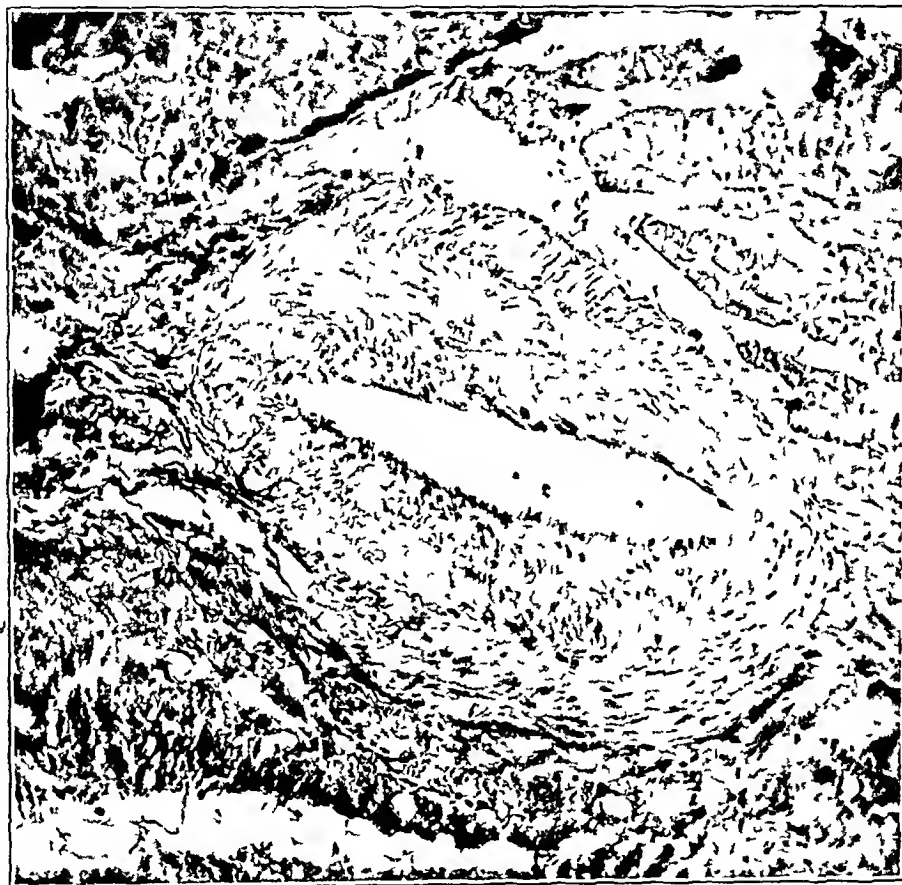


Fig 3—Swelling and cellular proliferation in a myocardial artery

TABLE 2—*Death and Survival Rates of Rabbits Given an Intravenous Injection of T-1824*

Dose per kilogram	1 cc	3 cc	5 cc	10 cc.
Death in 1 to 24 hours	0	11%	0	0
2 to 14 days	12%	33%	33%	50%
2 weeks to 3 months	35%	22%	33%	0
Survival	50%	33%	33%	50%
Total number of animals	5	9	6	4

less extensive and advanced hepatic, renal and cardiac lesions were found in 2 of the 5 cats killed six months after the injection of the dye. The organs of the other 2 animals of this group were normal.

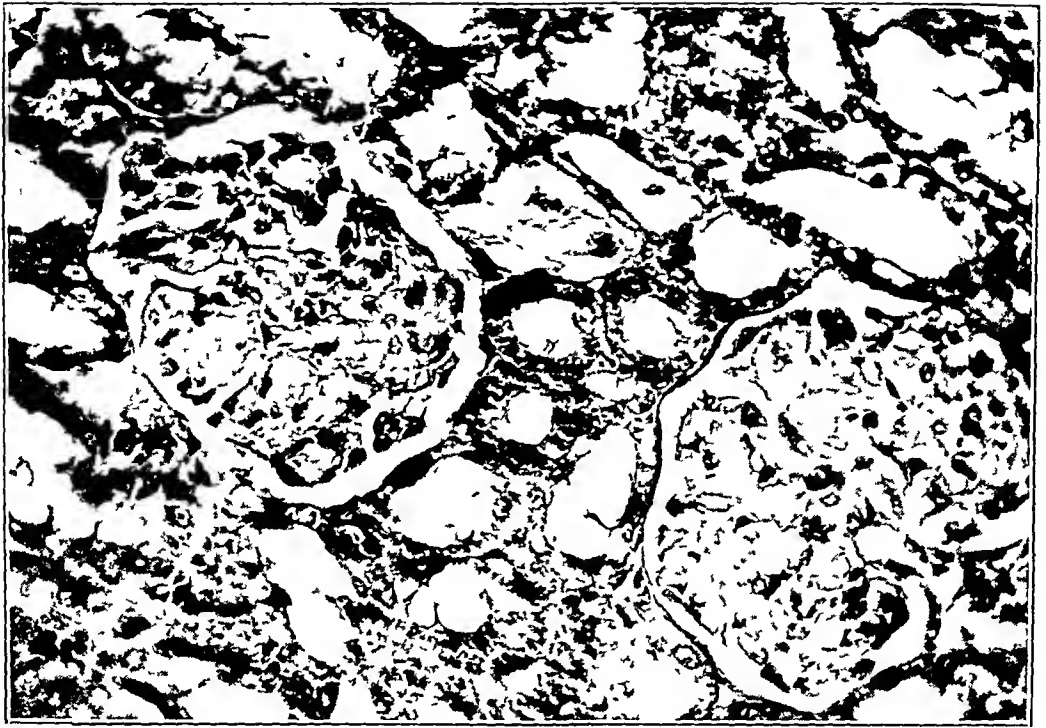


Fig 4—Extensive hyaline deposition in glomerular tufts

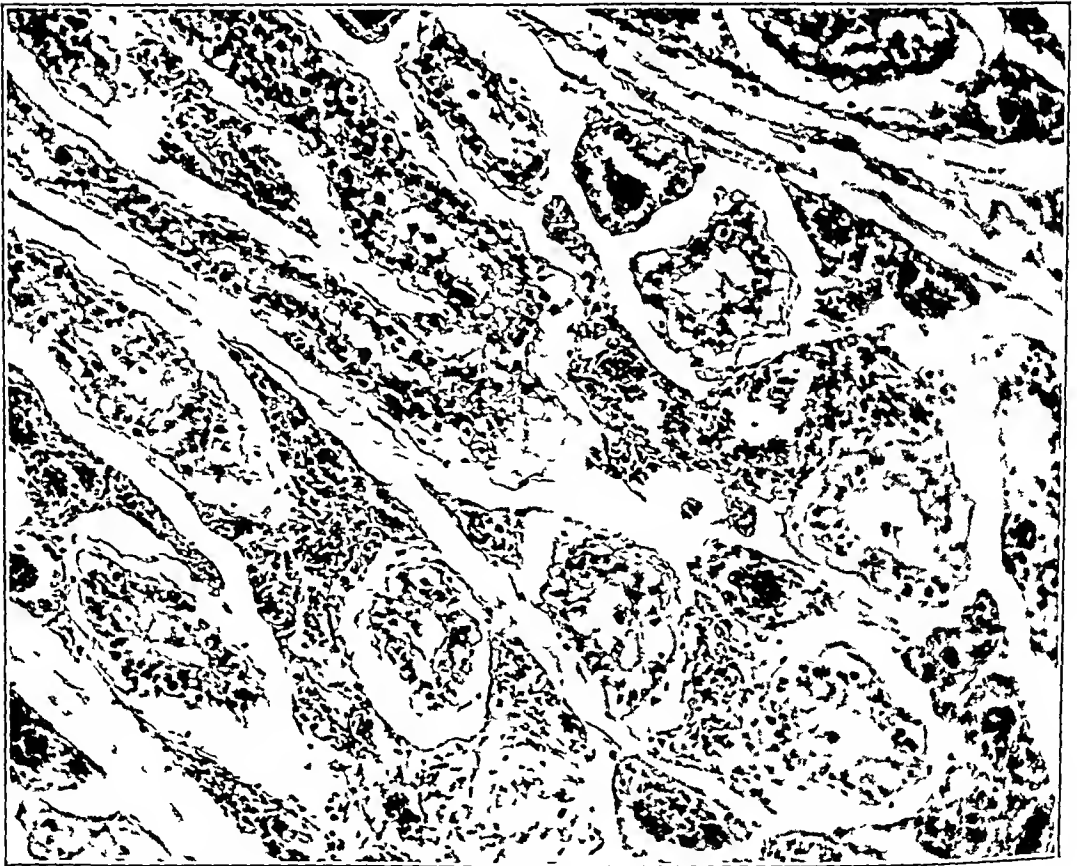


Fig 5—Considerable atrophy of the seminiferous tubules with lymphocytic infiltration and congestion of the interstitial tissue

Intravenous Injection of Dye T-1824 into Rabbits—Twenty-seven rabbits were given an intravenous injection of a 0.5 per cent Evans blue solution. Histologic examinations were made of the organs of 9 of these rabbits. Eight rabbits received 1 cc per kilogram, 9 rabbits 3 cc, 6 rabbits 5 cc and 4 rabbits 10 cc. The dye was not demonstrably excreted in an unchanged form in the urine and the feces. The toxicity of the dye to rabbits is illustrated in table 2, which gives the death rates and survival times.

The relation between the dose of dye administered, on the one hand, and the mortality rate and the survival time, on the other, is not quite as clearcut as in the cats. Nevertheless, the series receiving 10 cc per kilogram showed the highest number of early fatal reactions.

Of the rabbits given 3 cc per kilogram, those which died within two hours after the injection showed at autopsy a large cheesy abscess in the mediastinum, involving the pericardial sac. The internal organs as well as the skin and the mucous membranes were deeply blue. Death evidently was caused by an aggravation of the existing circulatory disturbances ensuing from the injection of the dye.

The rabbits which died within two to fourteen days after the administration of the dye had intensely blue internal organs, skin and mucous membranes. The brain was unstained, the meninges were blue. The lungs were congested and edematous and in some rabbits showed hemorrhagic areas or were surrounded by fibrinous pleurisy. The left side of the heart was contracted, and the right, which was discolored bluish, was dilated. The axillary and auricular lymph nodes were blue, as were the liver, the stomach, the intestine, the spleen, the adrenal glands, the kidneys, the blood vessels and the cartilage of the ribs. The testes were small, flabby and deep blue.

In the group of 7 rabbits which died two weeks to three months after the injection 3 showed at autopsy a cheesy abscess in the mediastinum, involving the pericardial sac or the lung. The lungs were congested and showed hemorrhagic areas. The renal cortex was slightly blue or slate blue. The liver was turbid and slightly blue in 2 rabbits, as was the cartilage of the ribs, the aorta, the spleen and the intestine. The testes of one of these 2 rabbits were distinctly blue. The other organs were of normal color and appearance.

In the group of 10 rabbits which were killed five to eleven months after the injection 1 exhibited slightly bluish skin and mucous membranes, while in 2 others the upper incisor teeth were distinctly blue. The testes were recorded as small and flabby in 2 rabbits. All other organs were grossly normal.

The histologic changes observed in the organs of these various groups were similar to those recorded for the corresponding groups of cats. The animals which died two days or more after the injection showed a loss of the nuclei in large ganglion cells of the brain stem and the medulla oblongata, associated with lysis of the Nissl substance. In several instances small accumulations of glia cells were noticed. The lungs were often edematous and congested and contained hemorrhagic areas. In 2 instances there was a concentric fibrous thickening of the intima of the larger and medium-sized intrapulmonary branches of the pulmonary artery. Small myocardial necroses or hyaline degenerations, together with fibrous scars and swelling and cellular proliferation in the wall of myocardial arteries, occurred in several animals (fig. 3). The liver often exhibited edema, congestion and sometimes degeneration or necrosis of liver cells. The renal tubules were usually more or less degenerated. In 2 rabbits there was marked hyaline thickening of the glomerular septums with degeneration of the cellular elements, while the distended cortical tubular lumens contained large albuminous casts (fig. 4). Similar hyaline deposits forming coarse networks in and around the follicles were present in the spleens of these animals. The testicular tubules of the 4 male rabbits of this group showed varying degrees of degenerative changes. These consisted of extensive atrophy of the seminiferous epithelium with collapse of the tubules, which were lined in such instances only by spermatogonia and Sertoli's cells, and in 2 instances, of a hyaline thickening of the basement membrane surrounding almost obliterated, empty lumens (fig. 5). The interstitial tissue was increased in amount in 2 instances and congested in 2 others.

Intravenous Injection of Dye T-1824 into Rats—A 0.5 per cent solution of T-1824 was injected into the tail vein in 20 rats. Five of these rats received 1 cc per kilogram, 5 rats 3 cc, 5 rats 5 cc and 5 rats 10 cc. None of the rats of the first two groups died as the result of the treatment. These rats were killed five to six months later. Of the 5 animals belonging to the third group (5 cc per kilogram), 1 died one month after the injection while 2 of the fourth group died within three months after the administration of the dye. The survivors were killed six months later. The rats tolerated the dye without any apparent immediate untoward effect and showed increase in weight during the observation period of six to six months.

The autopsy of the animals which died showed a blue subcutaneous tissue, particularly in the tail, and definitely blue internal organs. Particularly the testes and epididymides were distinctly blue. The lungs were hemorrhagic. The glandular part of the gastric mucosa was blue, while the squamous cell portion was unstained. The brain showed bluish spots only within the vascular network. The postmortem examination of the rats which were killed often revealed the testes and epididymides to be colored blue or green. The adrenal glands sometimes had a bluish cast.

The histologic examination of the organs of the rats which died from the toxic action of the dye disclosed congestion of and hemorrhages into the brain, which were occasionally associated with pyknosis of Purkinje's cells. The lungs were edematous and congested and contained hemorrhagic or pneumonic foci. The pulmonary arterioles of one rat had swollen and partly hyaline walls. There was often congestion or even interstitial edema of the myocardium, which was accompanied in one instance by a scanty accumulation of leukocytes, while in a second case purulent pericarditis was found. The aorta was normal. The liver



Fig 6—Complete degeneration of the epithelium of the seminiferous tubules with massive calcium concretions in the empty tubular lumens

usually showed congestion and some degree of liver cell degeneration. The seminiferous epithelium of the testes was desquamated and atrophic in several instances and contained multinucleated giant cells.

The organs of the rats which were killed were in general normal with the exception of the testes. In about 50 per cent of the 14 examined rats these exhibited more or less severe degenerative lesions of the epithelium of some, many or all of the seminiferous tubules, such as almost complete loss of the cellular lining, collapse of the tubules with hyaline thickening of the basement membrane, large and numerous calcium concretions in the lumens and once in the vascular walls (fig 6).

Inasmuch as these testicular lesions were of definite interest, especially as they appeared as early and late manifestations in testes which had retained an appreciable amount of dye over a period of five to six weeks and were found in dogs, rabbits and rats, 25 male rats, 4 months old, were given two intraperitoneal injections of 1 cc of a 1 per cent dye solution. There was an interval of three days between the two administrations. Seventeen of the rats

died within fourteen days, and the 8 survivors were then killed. The organs, including the testes, were deep blue in all animals. The histologic examination of the testes of these 25 rats showed that 43 per cent had a degenerative testicular lesion, which was moderate to severe in 23 per cent of the 25 rats, indicating that an actual toxic effect of the dye was present, as testicular degenerations occur spontaneously only relatively rarely in rats of this age and are then usually of minor degree (Hueper)

COMMENT

The experiments indicate that the minimal lethal dose of T-1824 given as a single intravenous dose of a 0.5 per cent solution is 10 cc per kilogram for dogs and cats. The dose is apparently somewhat higher for rabbits, as only 50 per cent of the rabbits died after the intravenous injection of 10 cc per kilogram, and is evidently still higher for rats, of which 40 per cent died after such a dose. It is characteristic for the action of the dye that, because of its prolonged retention in the various organs, it may cause death after a delay of several weeks or even months. This observation is of importance in adjudging the toxic qualities of the dye, as the claim has been made that even large amounts of the dye are not toxic (Gibson and Gregersen⁵, Price and Longmire^{3c}). The immediate toxic effects after intravenous injection of the dye consist of vomiting, diarrhea and prostration. The demonstrable excretion of the dye with the urine and the feces ceased two to four days after the injection. While Price and Longmire^{3c} demonstrated its presence in the bile of dogs, none was found in the bile of the cats studied.

Among the vitally important organs the heart, the liver and the lungs are the most severely damaged and show cellular degenerations and necroses, usually in association with increased vascular permeability (edema, hemorrhage, cellular exudation). Less extensive injury is present in the brain and the renal tubules. Among the significant acute as well as chronic lesions degenerative changes of the spermatogenic epithelium of the testicular tubules is a common and striking feature. It may be possible also that the hyaline deposits found in the glomeruli and spleens of several rabbits are related to some interaction of the dye with plasma proteins, as Rawson² has shown that eight dye molecules combine with one serum albumin molecule and thereby evidently change its size, shape and diffusibility. Gregersen and Rawson¹ stated that the dye-serum albumin combination diffuses from the blood stream at approximately the same rate as antibody globulin and maintains this bond when present in the tissue fluids. Whether or not the degenerative medial and sclerotic intimal changes found in the aorta and the pulmonary arterial branches of some of the dogs, rabbits and rats are connected with such a plasma protein disturbance remains uncertain but not improbable.

SUMMARY AND CONCLUSIONS

The dye T-1824 (Evans blue) exerts a lethal effect on dogs and cats when introduced intravenously as a 0.5 per cent aqueous solution in amounts of 10 cc per kilogram. The injection of smaller doses by this route (3 cc and 5 cc per kilogram) may cause delayed death in some of the animals thus treated.

The mortality rate and the survival time are a function of the dose.

Death occurring several weeks to months after the introduction of doses not causing acute death (within one to two days) is related to the prolonged retention of appreciable amounts of the dye in the tissues of various organs, particularly the testis, the epididymis, the adrenal glands, the liver, the kidneys, the periaortic connective tissue, the teeth and cartilage).

⁵ Gibson, I. G., and Gregersen, M. Toxicity of Two Vital Dyes Used in Plasma Volume Determinations, *Am J Physiol* **113** 50, 1935.

The heart, the liver, the lungs and the testes show the most marked degenerative effect of the dye, while the brain and the kidneys exhibit less severe regressive lesions, the development of which is associated with increased vascular permeability

The clinical administration of the dye in amounts of 5 cc of a 0.5 per cent or 1 per cent solution to the individual patient is apparently a safe procedure. However, the occurrence of late fatalities among animals given 1 cc per kilogram of a 0.5 per cent solution is an indication that caution should be exercised with the repeated administration of this dye to human beings so as to avoid possible toxic effects

113 West Eighteenth Street

THE GOITER HEART

AN EXPERIMENTAL STUDY

C ALEXANDER HELLWIG, M D

WICHITA, KAN

While it is generally believed that cardiac disturbances in patients with goiter are caused by hyperthyroidism attention has been called recently to heart disease in goitrous patients who do not present symptoms of increased thyroid function Davison¹ designated this condition as "masked hyperthyroidism" He assumed that adenomas are for years spilling over into the circulation toxic products which though not sufficient to produce an increase of the basal metabolic rate at any time, cause low grade toxemia which ultimately produces heart disease

Hertzler,² on the other hand, denied that cardiac disturbances in patients with long-standing goiter are due to hyperthyroidism and expressed the belief that the colloid in old goiters degenerates and forms a substance which when resorbed acts specifically on the heart muscle He found that this degenerated colloid stains orange with Mallory's aniline blue method in contrast to the blue-stained colloid in exophthalmic goiter

Schmidt³ demonstrated in the colloid of degenerated goiters an organic iodine-containing substance other than thyroxin and by injecting extracts of goiters into thyroidectomized rats he produced an increase in the heart rate without a corresponding increase in the basal metabolic rate

In regard to these recent studies it is well to remember that the conception of goiter heart originated more than one hundred years ago in Alpine countries where toxic goiter is extremely rare (Adelmann,⁴ 1828) It was in Tyrol, Austria, where Schranz⁵ in 1887 formulated the often quoted sentence "The ultimate fate of the patient with goiter depends on his heart He dies of myocardial degeneration"

In Aarau, Switzerland, where exophthalmic goiter was observed in less than 5 per cent of the cases in which goiter had been treated surgically, Bircher⁶ encountered cardiac complications in 70 per cent of his surgically treated goitrous patients For goiter heart without hyperthyroidism no satisfactory explanation has been found Neither the theory of "mechanical goiter heart," which explains the cardiac symptoms by pressure of the goiter on the trachea large blood vessels or the vagosympathetic nerves, nor the theory of "torpid goiter heart," which makes hypofunction of the enlarged thyroid gland responsible, has found general approval (Crotti⁷) All investigators seem to have agreed only on one point, namely, that

From the Department of Pathology, St Francis Hospital

1 Davison, T C Thyroid Surgery in Cardiac Patients, South Surgeon **3** 103 1934

2 Hertzler, A E Surgical Pathology of the Thyroid Gland Philadelphia, J B Lippincott Company, 1936, p 130

3 Schmidt, C R, and Hertzler, A E Cardiotoxic Goiter A Distinct Entity, Endocrinology **31** 684, 1942

4 Adelmann Beiträge zur Pathologie des Herzens, der Schilddrüse und des Gehirns Jahrb d phil-Med Gesellsch zu Würzburg **1** 104, 1828

5 Schranz, J Beiträge zur Theorie des Kropfes, Arch f klin Chir **34** 91 1886-1887

6 Bircher, E Beiträge zur Kropfrage II Die toxische Struma (Kropfherz und Jodbasedow), Beitr z klin Chir **141** 580, 1927

7 Crotti, A Diseases of the Thyroid Parathyroids and Thymus Philadelphia Lea & Febiger, 1938 p 676

there is no anatomic type of goiter which predisposes to cardiac complications. Diffuse as well as nodular, parenchymatous as well as colloid, cancerous as well as noncancerous goiter has been found associated with goiter heart (Wegelin⁸).

In contradistinction to the great number of clinical observers who have reported on goiter heart, experimental pathologists have contributed little to this interesting subject. During the last twenty years no paper on the heart in experimental goiter without hyperthyroidism has appeared in the literature.

EXPERIMENTAL DATA

My experiments were begun on Aug 15, 1942. Seventeen male and 13 female white rats of the Wistar strain, 3½ months old, were divided into three groups. Each group was

TABLE 1—Data Showing no Correlation of Weight of Heart with Size of Thyroid Gland

Rat	Sex	Weight Gm	Heart Weight Gm	Relative Heart Weight	Size of Thyroid Gland, Mm	
					Left Lobe	Right Lobe
Experimental Group 1 Yellow Corn and Oats Pure Water						
1	M	390	1.710	4.4	6.5 by 2.5	8 by 4
2	M	298	1.365	4.6	6 by 3.5	6 by 4
3	M	278	1.250	4.5	4 by 2.5	4 by 3
4	M	338	1.320	3.9	6.5 by 3.5	6.5 by 3
5	M	278	1.050	3.8	5 by 2.5	5 by 3
6	M	278	1.400	5.2	5 by 2.5	4 by 3
7	M	320	1.770	5.5	6 by 3	6.5 by 3
8	F	314	1.140	5.1	5 by 3	5 by 3
9	M	314	1.300	4.1	4.5 by 2.5	4.5 by 2.5
10	M	344	1.500	4.4	6 by 2.5	6 by 3
11	F	298	1.370	4.6	5.5 by 3	5.5 by 3
Experimental Group 2 Yellow Corn and Oats 1 per Cent Solution of Calcium Chloride						
1	M	270	1.190	4.4	5.5 by 4	5.5 by 4
2	F	212	1.210	5.7	4.5 by 2	5.5 by 2
3	M	306	1.280	4.2	5 by 3	6.5 by 3
4	F	230	1.230	5.4	6 by 3	7 by 4
5	M	310	1.460	4.7	6 by 2.5	5.5 by 3.5
6	F	222	1.355	6.1	7 by 3	7 by 4
7	F	290	1.390	4.8	5 by 3	5 by 4
8	M	296	1.625	5.5	5 by 3	5 by 4
9	F	238	1.075	4.5	6 by 3.5	5 by 3
10	F	180	1.317	5.7	6.5 by 2	6 by 3
Control Group Balanced Diet of Purina Chow and Pure Water						
1	M	184	1.010	5.4	5 by 2	6 by 2
2	F	264	1.110	4.2	3 by 2	4 by 2
3	F	210	1.070	5.1	5 by 2	4 by 2.5
4	M	366	1.520	4.2	5 by 2	5 by 3
5	M	400	1.750	4.4	5 by 3	5 by 3
6	F	246	1.100	4.5	3.5 by 2.5	4 by 2
7	M	400	1.610	4.0	5 by 3	5 by 3
8	F	324	1.370	4.2	5 by 3	4 by 3
9	F	250	1.155	4.6	4 by 2.5	5 by 4

housed in a Dorrer cage with floors of mesh wire and without bedding material. The first group, consisting of 9 males and 2 females, received the goitrogenic diet of Wegelin,⁹ i. e. a mash of cornmeal and rolled oats boiled in water. As drinking water, pure well water was given. The food was freshly prepared every day. The second group, consisting of 5 males and 5 females, was fed the same diet, however, as drinking water, a 1 per cent solution of calcium chloride was given. The high goitrogenic effect of this calcium-rich intake had been demonstrated in several earlier experiments.¹⁰ Four males and 5 females were

8 Wegelin, C. Schilddrüse, in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, p. 426.

9 Wegelin, C. Zur experimentellen Kropfforschung, *Schweiz med Wchnschr* **57** 848, 1927.

10 Hellwig, C. A. Experimental Goiter Due to Calcium, *Arch Surg* **40** 98 (Jan) 1940. Experimental Goiter Functional, Chemical and Histologic Studies, *Arch Path* **19** 364 (March) 1935.

kept as controls and received a well balanced stock diet of Purina 10X checkers¹⁰¹ and pure drinking water

The rats of all three groups remained in excellent health throughout the experiment, and no death occurred. During the four months of observation 69 rats were born in the three cages, namely, 14 in the first, 23 in the second and 31 in the control colony. The newborn animals were killed with chloroform immediately after birth and preserved in 4 per cent solution of formaldehyde for further study.

The feeding experiment was continued for one hundred and twenty-six days. Then the 30 adult animals were killed with chloroform and immediately examined. After the body weight had been determined, complete dissections were made of each animal. The heart was removed by cutting the great vessels at a constant level. All the blood contained in the cardiac chambers was allowed to drain out, and then the heart was weighed. The thyroid gland was removed together with the trachea, and the measurements of both lobes were taken. The organs were at once placed in 4 per cent solution of formaldehyde. Paraffin sections were made from the thyroid glands and hearts of all animals, and different staining methods were employed. From the hearts frozen sections were also made and stained for lipid with sudan.

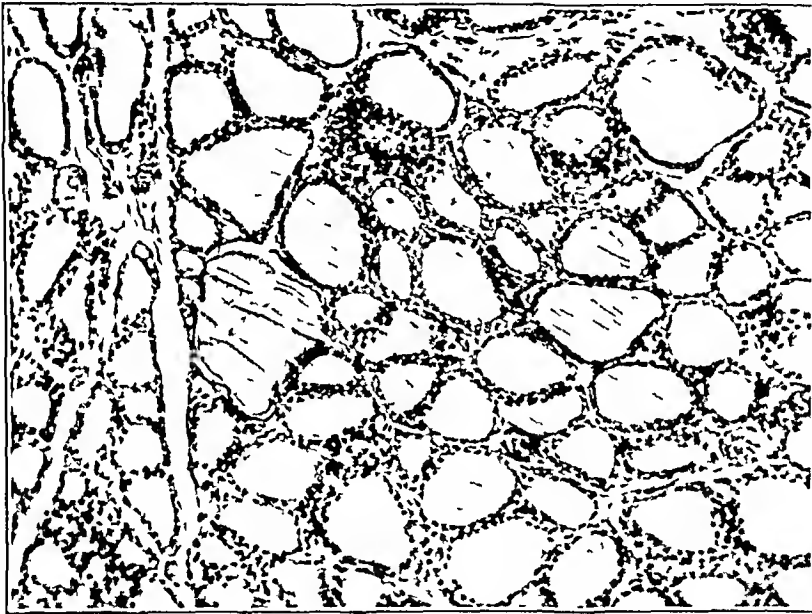


Fig 1—Normal thyroid gland of a white rat of the control group. Note the large colloid filled acini.

RESULTS

Thyroid—From table 1 it is evident that the animals of groups 1 and 2 had definite goiters and that the thyroid glands of the control group were normal. The calcium-rich intake of the second group was definitely more goitrogenic than the pure water and the Wegelin diet consisting of cornmeal and oats. While in the controls the average length of one lobe of the thyroid gland was 4.4 mm, 6 rats of the second group had a length exceeding 5 mm, and the average was 5.5 mm.

¹⁰¹ Purina 10X checkers contains: crude protein not less than 20, crude fat not less than 3, crude fiber not more than 6, ash 8.5 per cent, nitrogen-free extract not less than 56. The ingredients are: wheat germ, dried skimmed milk, animal liver meal, brewers' dried yeast, barley malt, fish meal, meat meal, alfalfa meal, corn grits, soybean oil meal, cereal feed (from corn and wheat), molasses, dried beet pulp, riboflavin supplement, vitamin A and D concentrates, 1 per cent steamed bone meal and 1 per cent iodized salt. It is manufactured by Purina Mills, Ralston Purina Company, St. Louis.

In the group with a calcium-rich intake 7 rats had lobes measuring more than 5 mm, the average being 5.7 mm.

Microscopic examination showed in the controls, as a rule, large acini with low cuboidal epithelium and with well stained colloid. The blood vessels were not



Fig 2—*A*, experimental goiter in a white rat of group 1 following a diet of yellow corn and oats and pure well water. Note moderate hyperplasia. *B*, experimental goiter in a white rat of group 2 following the same diet and, as drinking water, a 1 per cent solution of calcium chloride. Note marked hyperplasia.

conspicuous (fig 1). Of the animals receiving the Wegelin diet, 2 showed marked and 9 moderate epithelial hyperplasia (fig 2 *A*), while in the group with a calcium solution as its drinking water 6 had marked (fig 2 *B*) and 4 moderate hyper-

plastic changes. The epithelium in the experimental goiters was high cuboidal the acini were small and contained either unstained or scanty fine granular colloid. The blood vessels were, as a rule, engorged with red blood cells. The gross and microscopic changes of these experimental goiters were identical with those found in former experiments.¹⁰ The function of the parenchymatous goiters proved to be slightly less than normal, and there was no chemical or metabolic evidence of hyperthyroidism. These goiters therefore resembled in structure and function the endemic goiter found in countries of high endemicity, i. e. Switzerland, the Himalayas and the Pyrenees.

Heart—In the control group the weight of the heart ranged from 1.010 to 1.750 Gm., the average being 1.268 Gm. In the first experimental group the heart

TABLE 2—Microscopic Changes in Thyroid Glands and Hearts of White Rats

Rat	Thyroid Gland Epithelial Hyperplasia	Heart		
		Lymphocytic Infiltration	Hyaline Degeneration	Scar.
Group 1				
1	Moderate	Present	Present	Present
2	Marked	Present	Absent	Present
3	Moderate	Present	Absent	Absent
4	Moderate	Absent	Absent	Absent
5	Moderate	Present	Absent	Absent
6	Moderate	Present	Present	Absent
7	Moderate	Present	Present	Present
8	Moderate	Present	Absent	Absent
9	Moderate	Present	Absent	Absent
10	Marked	Present	Absent	Absent
11	Moderate	Present	Absent	Absent
Group 2				
1	Marked	Present	Absent	Absent
2	Moderate	Present	Absent	Absent
3	Marked	Present	Absent	Absent
4	Marked	Present	Absent	Absent
5	Marked	Present	Absent	Absent
6	Moderate	Present	Absent	Absent
7	Marked	Present	Present	Present
8	Moderate	Absent	Absent	Absent
9	Moderate	Present	Absent	Absent
10	Marked	Absent	Absent	Absent
Group 3 (Controls)				
1	Absent	Present	Absent	Absent
2	Absent	Present	Absent	Absent
3	Absent	Present	Absent	Absent
4	Absent	Present	Absent	Present
5	Absent	Present	Absent	Absent
6	Absent	Present	Absent	Absent
7	Absent	Present	Absent	Absent
8	Absent	Present	Absent	Absent
9	Absent	Present	Absent	Absent

weight was between 1.050 and 1.770 Gm., with an average of 1.380 Gm. In the group with calcium-enriched drinking water the heart weight varied from 1.075 to 1.625 Gm., and its mean was 1.317 Gm.

Since in the experimental groups the body weight varied greatly, from 140 to 400 Gm., the absolute heart weight was much less significant than the heart weight in relation to the body weight. The ratio of the heart weight to the body weight was obtained by dividing the body weight into the heart weight modified by an appropriate shift of the decimal point ($1,000 \times \frac{\text{heart weight}}{\text{body weight}}$). The heart-body weight ratio of the animals of the first group was on the average 4.6, that of the group with calcium added to the drinking water was 5.05 and that of the controls was 4.5. Thus it is evident that the second experimental group of animals with the high calcium intake, showed a definite increase in the relative heart weight. In the first group the left wall of the heart measured on the average 3.8 mm. in

thickness, in the second, 4.4, and in the control group, 3.5 mm. The wall of the right ventricle measured 1.5, 1.1 and 1.3 mm, respectively. Therefore only in the calcium group was an increase in muscle substance of the left ventricle noticed. There was no correlation between relative heart weight and size or degree of hyperplasia of the thyroid gland.

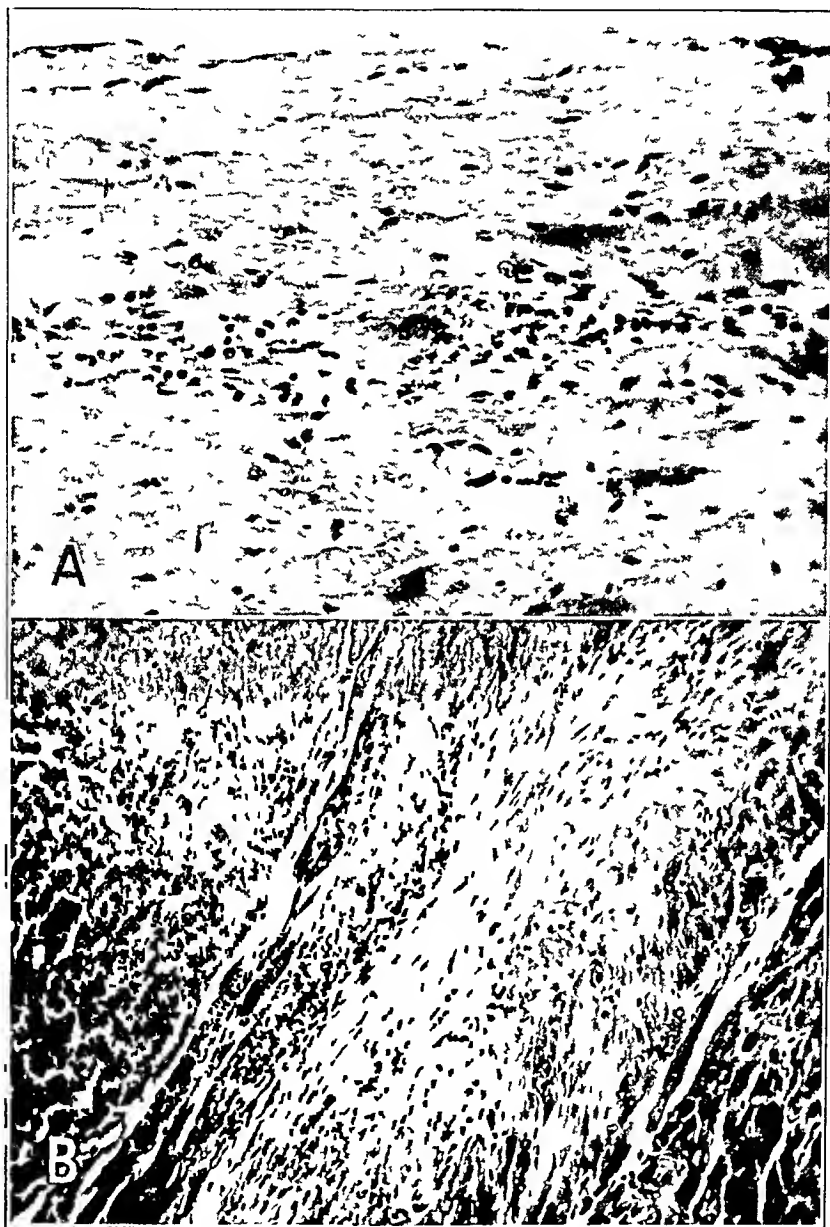


Fig 3—*A*, groups of lymphocytes in heart muscle of a goitrous rat. *B*, young scar in the myocardium of a goitrous rat.

The microscopic changes in the cardiac sections which included both ventricles, the septum, both atria, and the origin of the great blood vessels, are summarized in table 2.

In the neighborhood of small blood vessels of the myocardium small groups of lymphocytes were frequently encountered (fig 3 *A*). In the same location two or

three deep-staining polygonal cells the so-called mast cells, were also found in several cases. In the myocardium of 1 animal of the control group eosinophilic cells were noticed. Another place of predilection for groups of lymphocytes was the connective tissue between the myocardium and the great blood vessels.

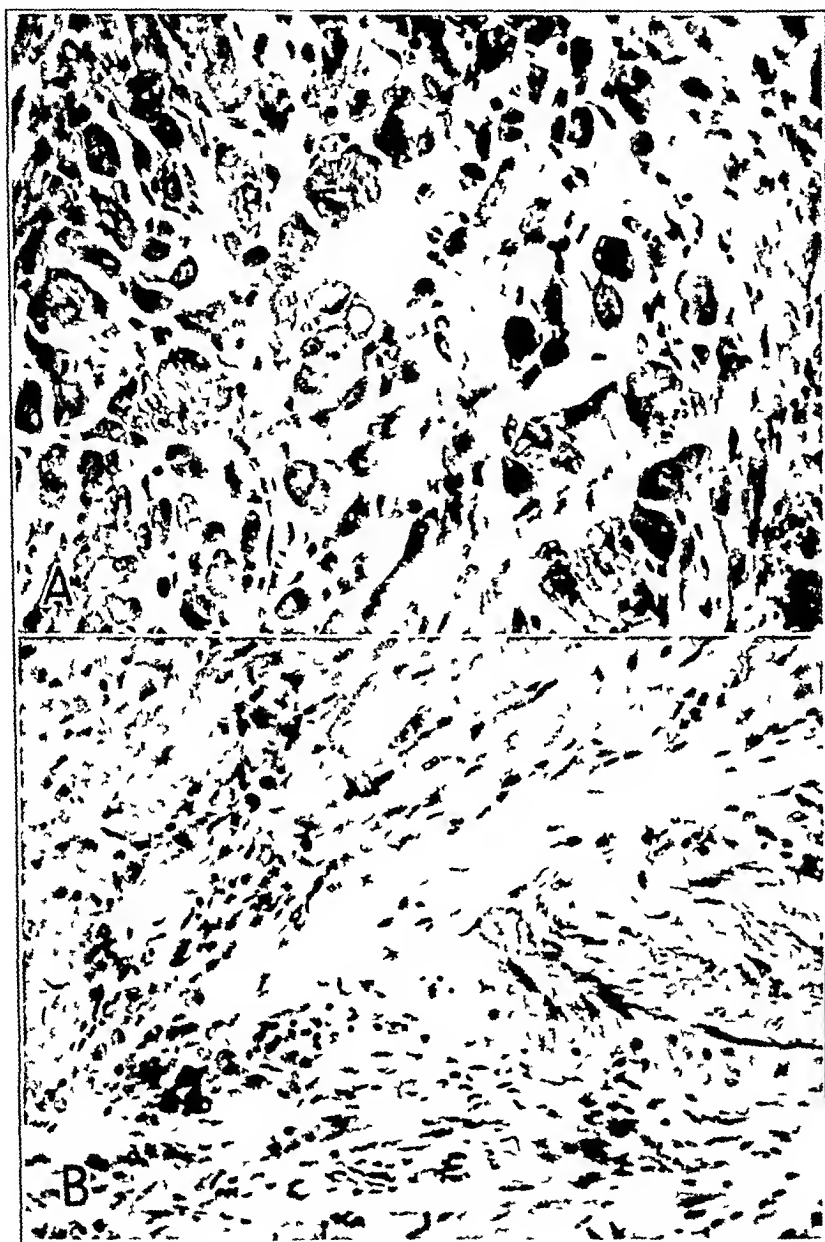


Fig 4—1, hyaline degeneration of muscle fibers in the heart of a goitrous rat. B, perivascular group of lymphocytes and mast cells in the heart of a control animal.

These lymphocytic groups in the myocardium were observed as often in the experimental animals of groups 1 and 2 as in the controls. Small scars in the myocardium were observed twice in the first group and once in the second, and a young scar with many fibroblasts was present in 1 animal of the control group (fig 3 B). Focal degeneration of muscle fibers (fig 4 1) with formation of

vacuoles in the sarcoplasm was found in 3 rats of the first group and in 1 animal of the group with calcium in the drinking water. Surprisingly enough, there was no difference in the occurrence of lymphocytic infiltration or scar formation between the animals with and those without goiter. Therefore the hyperplastic changes in the thyroid glands themselves cannot be held responsible for these histologic changes in the hearts. Since the animals of all groups showed identical myocardial lesions, it seems plausible that mild intercurrent infections, which are common in white rats, were the reason for them.

COMMENT

In 1911, Bircher¹¹ reported cardiac lesions in white rats in which large goiters had developed after these rats received water from a region in which goiter was endemic. Almost all of his experimental animals showed great enlargement of the heart with hypertrophy of the left ventricle and dilatation of the right ventricle. Microscopic study revealed in 22 of his 30 experimental animals fragmentation, cloudy swelling and fatty degeneration of the cardiac muscle fibers. There was also interstitial infiltration of the myocardium by leukocytes, in the late stages there was scar formation. Bircher did not find any correlation between these lesions of the heart and the size or the structure of the experimental goiters. He therefore concluded that the inflammatory and degenerative changes in the heart were due not to a direct effect of increased or perverted thyroid secretion but to an unknown goitrogenic agent which caused the enlargement of the thyroid gland and at the same time damaged the heart muscle. In Bircher's opinion, goiter heart in regions in which goiter is endemic is one of the manifestations of the cretinoid degeneration and may occur either alone or combined with other signs of this constitutional disorder—namely, endemic goiter, endemic deafness and endemic idiotism.

The only other investigator who studied the heart in animals with experimental goiter was Wegelin.⁸ He also observed enlargement of the heart in goitrous white rats due either to dilatation of the cardiac chambers or to muscular hypertrophy. His histologic observations in the enlarged hearts were mostly negative. Only in 3 of his 14 goitrous animals were small groups of lymphocytes and fibroblasts present in the myocardium. In one heart Wegelin found a distinct scar and in another vacuoles in the sarcoplasm. Wegelin concluded from these findings that simple endemic goiter has no toxic effect on the heart muscle.

My own experiments show that the myocardial changes described by Bircher occur frequently in the hearts of goitrous animals without hyperthyroidism. However they are present as often in white rats without goiter. Therefore they cannot be attributed to some toxic action of the goiter on the myocardium.

The hypertrophy of the left ventricle which developed in the goitrous animals given a calcium-rich water but not in the goitrous animals whose intake of food and water was calcium poor suggests excess of calcium as the causative factor. Two possible explanations present themselves. Chambers and Reznikoff¹² demonstrated that calcium chloride increases the viscosity of protein emulsions, and it is reasonable to assume that an excess of calcium in the experimental intake increased the viscosity of the blood plasma so that greater resistance was offered to the heart in circulating the blood. Secondly, it is well known (Howell¹³) that

11 Bircher, E. Weitere histologische Befunde bei durch Wasser erzeugten Rattenstrumen und Kropfherzen, *Deutsche Ztschr. f. Chir.* **112** 368, 1911.

12 Chambers and Reznikoff, cited by West, E. S. *Physical Chemistry for Students of Biochemistry and Medicine*, New York, The Macmillan Company, 1942, p. 278.

13 Howell, W. H. *A Textbook of Physiology*, ed. 14, Philadelphia, W. B. Saunders Company, 1940, p. 570.

calcium causes more forceful contractions of the heart muscle. Both of these pharmacologic effects of calcium may produce work hypertrophy of the left ventricle. If one accepts a direct effect of the positive goitrogenic factor—calcium excess—on the heart as the cause of goiter heart, which manifests itself as left ventricular strain, it is easily understood that there is no anatomic type of goiter which predisposes to cardiac complications.

SUMMARY AND CONCLUSIONS

In experimental studies planned to determine whether anatomic changes can be demonstrated in the hearts of animals with simple goiter, no histologic changes were found in the hearts of goitrous animals which would suggest a direct toxic effect of goiter on the myocardium. Lymphocytic infiltration, degeneration of muscle fibers and scar formation were common in the hearts of the experimental animals, but since they were as often encountered in the hearts of the nongoitrous controls, they have to be explained by causes which were active in all three groups, possibly some intercurrent infection.

The only positive anatomic finding was a significant hypertrophy of the left ventricle in the animals which received a calcium-rich diet. This observation suggests that left ventricular strain in endemic goiter may be due to a direct effect exerted on the heart muscle by the same factor which is responsible for the development of goiter—for instance, an excess of calcium in the food.

The results of my experiments are in accord with the experience of most observers that there is no anatomic type of endemic goiter which predisposes to cardiac complications.

HYPOPROTEINEMIA

THE CLINICAL RELATIONSHIP OF PROTEINS AND THE PROTEIN METABOLISM TO THERAPY WITH SPECIAL REFERENCE TO SURGERY

ABRAHAM O WILENSKY, M D
NEW YORK

This communication will concern itself with the increasing clinical importance of the proteins and protein metabolism in medicine, especially in surgery, and the relationship of hypoproteinemia to apparent and to latent hepatic parenchymal disease. Necessarily it will include a review of all of the available knowledge concerning this branch of normal physiology and of the aberrations of function which occur in disease. It will indicate the extent to which these obtainable data can be used (1) in the corroboration of diagnoses, (2) in the possibility of estimating the degree and the extent of anatomic change, (3) in prognosis and (4) in the evaluation of the risk of contemplated operations. Finally, it will include (5) criteria on which the newer therapeutic measures can be employed.

PROTEIN METABOLISM

The importance of the quantity and the quality of dietary protein for the nitrogen requirements of the body and for the maintenance of good health has been repeatedly demonstrated. In many cases variable interrelationships with other dietary factors have been observed, but the reported experiences have emphasized nevertheless the numerous and often unsuspected ways in which the protein fractions are of importance to the body.

Formation and Storage of Plasma Proteins—The vast amount of experimental work has not provided as clear a picture of the formation and the fate of the plasma proteins in the organism as one would like. The cycle of the formation of plasma proteins revolves around the liver from three standpoints: production, storage and renewal. Plasma fibrinogen and plasma albumin seem to be formed exclusively in the liver. Plasma globulin is formed mainly in the liver but also to some extent by the reticuloendothelial system (Kerr, Hurwitz and Whipple¹). After the amino acids reach the liver by the portal vein from the intestinal tract, they are built partly into proteins and partly into plasma protein-building material. A portion of this synthesized material is placed in physically undemonstrable reserve stores of plasma proteins, distributed mainly in the liver and to a lesser extent in many other tissues. The fully formed and fixed protein in the body cells is never available in time of stress or even otherwise for the formation of plasma proteins. The dispensable reserves of proteins include a sufficient store which is instantly available for use and another supply which is less readily available, and both of these together are sufficient to form plasma proteins of a quantity equal to or greater than that usually present in the circulating blood. All of this storage is a function of the liver, and there is evidence to show that the albumin, globulin and fibrinogen fractions of plasma all form part of a single loosely bound protein system.

The various protein fractions of blood plasma are regenerated during a period of fasting and after acute depletion, as in hemorrhage as well as during the normal

¹ Kerr, W. J., Hurwitz, S. H., and Whipple, G. H. Regeneration of Blood Proteins. *Am J Physiol* 47: 336, 370 and 379. 1918.

wear and tear of the tissues. This was first observed by Morawitz and was later studied by other investigators, particularly Whipple and his associates. During conditions of health and of "well being" proteins are present in human plasma to the extent of 6.5 to 7.5 Gm per hundred cubic centimeters, with albumin and globulin fractions in the ratio of about 1.6 to 1.

In conditions of health the blood plasma level of proteins bear an approximately constant relation to the fixed tissue protein supplies in the body. During conditions of disease or undernourishment this proportion is kept up at the expense of the reserve supply, and although the protein relation of plasma to tissue may still be at a fairly normal average, the protein reserves may be more or less depleted. This was well illustrated in the following case.

CASE 1—A 50 year old woman had a severe form of thyrotoxicosis (basal metabolic rate, +75). She had moderate diarrhea and continuously lost weight even though the diet approached approximately 3,500 calories per day. There was no doubt that the reserve supply of proteins was being diminished, and the total plasma protein level was 5.77 Gm per hundred cubic centimeters as determined by the falling drop method at a specific gravity of 1.0243.

Renewal of Plasma Proteins—The replacement of the plasma proteins takes place from two sources: (1) exogenous—from ingested food—and (2) endogenous—from the reserve stores of plasma protein-building material. Experimental investigations have indicated that not only the quantity but also the quality of the food proteins is of the utmost importance in the production and the regeneration of the various plasma proteins.

The usual human diet contains varying amounts of protein from animal and vegetable sources. The various animal and vegetable proteins differ in nutritive value, particularly in potential amino acid content and in content of those individual amino acids (valine and methionine) which have been proved indispensable.

The known amino acids are

A Essential	B Nonessential
1 Lysine	1 Glycine
2 Tryptophan	2 Alanine
3 Histidine	3 Serine
4 Phenylalanine	4 Norleucine
5 Leucine	5 Aspartic acid
6 Isoleucine	6 Hydroxyglutamic acid
7 Threonine	7 Proline
8 Methionine	8 Hydroxyproline
9 Valine	9 Citrulline
10 Arginine	10 Tyrosine
	11 Glutamic acid
	12 Cystine

Amino acids that cannot be synthesized by the body are tyrosine, tryptophan, lysine, cystine, histidine, arginine and glutamic acid. Deficiency in even one of the amino acids that are essential for the construction of tissues limits the value of a protein to the animal body. A number of proteins occurring in foods are deficient in one or more of the essential amino acids. For example, diets which consist mostly of milk are insufficient for maintenance and growth since cystine, which cannot be synthesized by the body, is entirely lacking, gelatin, although rich in glycine (an amino acid that may be synthesized by the body), does not contain tryptophan and valine (essential amino acids) or tyrosine and hydroxyglutamic acid, which are nonessential. Ovalbumin also is lacking in several amino acids. The amino acids in fish and meat measure up favorably with the requirements for normal maintenance and growth. Generally speaking, animal proteins contain all

or nearly all of the essential amino acids, and vegetable proteins do not. But one can obtain similar results and effects by supplementing the various vegetable proteins with one another, with or without the addition of prepared amino acids until the total amount is adequate. Under such circumstances the animal proteins are not absolutely necessary. Customarily, however, human beings prefer a diet containing a large amount (more than half) of the protein ingested from animal sources. In any case the plasma proteins can be synthesized only if the body receives the proper mixture of amino acids.

In the final analysis the customary and normal plasma protein level is dependent on the continued ingestion of material which can be utilized for the formation of new plasma proteins. Hypoproteinemia and edema due to malnutrition illustrate this ultimate dependence of the plasma proteins, like other similar compounds in the body, on exogenous sources.

In the light of present evidence it seems, moreover, that plasma protein does not remain static after being elaborated but participates in a dynamic equilibrium with the reserve protein of the body, as suggested by Madden and Whipple,² and that the normal balance results from the continuous ebb and flow between the old and the new in the continuation of the normal metabolic activity.

Protein Enrichment of the Liver—Experimental evidence has accumulated (Pflüger,³ Seitz,⁴ Addis and his co-workers⁵ and others) regarding the importance of the protein enrichment of the liver which follows the administration of high protein diets. This is associated not only with hyperplasia or hypertrophy but also with an increase in the content of protein per unit weight of tissue. Contrariwise, the relative loss of protein during abstention from food is greatest for the liver. The studies of Luck⁶ show that all the hepatic proteins, including albumin, euglobulin and pseudoglobulin, participate equally in the process of storage.

Blood-Clotting Elements and Blood-Clotting Function—The blood-clotting elements and the blood-clotting function are intimately bound up with the formation and the renewal of the plasma proteins. Normally the liver forms the fibrinogen fraction of the plasma proteins. Fibrinogen is the soluble precursor of the insoluble fibrin. The blood plasma normally contains about 250 mg per hundred cubic centimeters of fibrinogen. This content varies under different circumstances, is apparently independent of the cellular content of the blood, corresponds proportionally to the sedimentation rate of the red blood cells and is decreased by severe damage of the liver and a diet deficient in protein.

Normally, also, the liver originates the vitamin K principle (Smith and co-workers,⁷ Warner,⁸ Warren and Rhoads⁹ and others).

2 Madden, S. C., and Whipple, G. H. Plasma Proteins. Their Source, Production and Utilization, *Physiol Rev* **20** 194, 1940.

3 Pflüger, E. Glykogen, *Arch f d ges Physiol* **96** 1, 1903.

4 Seitz, E. Die Leber als Vorrathskammer für Eiweissstoffe, *Arch f d ges Physiol* **111** 309, 1906.

5 Addis, T., Lee, D. D., Lew, W., and Poe, L. J. The Protein Content of the Organs and Tissues at Different Levels of Protein Consumption, *J Nutrition* **19** 199, 1940.

6 Luck, J. M. Liver Proteins. The Question of Protein Storage, *J Biol Chem* **115** 491, 1936.

7 Smith, H. P., Warner, E. D., and Brinkhous, K. M. Prothrombin Deficiency and Bleeding Tendency in Liver Injury (Chloroform Intoxication), *J Exper Med* **66** 801, 1937.

8 Warner, E. D. Plasma Prothrombin. Effect of Partial Hepatectomy, *J Exper Med* **68** 831, 1938.

9 Warren, R., and Rhoads, J. E. Hepatic Origin of Plasma-Prothrombin. Observations After Total Hepatectomy in Dog, *Am J M Sc* **190** 193, 1939.

The hepatic cell also forms prothrombin in the presence of adequate vitamin K activity, and with thromboplastin and calcium it forms thrombin. After severe parenchymal damage the liver is unable to form prothrombin even when sufficient vitamin K is available.

As a test of the functional capacity of the liver cell and indirectly of the degree and the location of the hepatic damage, these three factors and the blood-clotting function as a whole are becoming of increasingly large value for clinical purposes. The fibrinogen and prothrombin levels (Wilson¹⁰) in the blood plasma are used by themselves as indications of the presence of hepatic damage (Quick¹¹, Butt, Snell and Osterberg¹², Brinkhous and Warner¹³, Stewart and Rourke¹⁴, Rhoads¹⁵; Lucia and Aggeler¹⁶, Pohle and Stewart¹⁷, Allen and Julian,¹⁸ and others).

According to Andrus,¹⁹ in patients in whom the prothrombin activity of plasma is depressed below 80 per cent of the normal as the result of obstructive jaundice, a rise of more than 10 per cent will occur within from forty-eight to seventy-two hours after the intramuscular administration of 2 mg of 2-methyl-1, 4-naphthoquinone (synthetic vitamin K). In patients with jaundice due to organic disease of the liver no such effect occurs, and in the absence of obstructive jaundice, biliary fistula or abnormal intestinal absorption the prothrombin level is an index of essential hepatic disease (Pohle and Stewart¹⁷). Experimentally, the prothrombin level in the blood plasma falls rapidly after partial or total hepatectomy (Warner⁸, Warren and Rhoads⁹, Andrus, Lord and Moore²⁰, Smith and co-workers⁷) after chloroform intoxication (Smith and co-workers⁷, Warner, Brinkhous and Smith²¹, Brinkhous and Warner¹³) and after chronic hepatic injury from carbon tetrachloride (Bollman, Butt and Snell²²).

Andrus, Lord and Moore²⁰ made the observation which I have repeatedly made with regard to all tests of hepatic function, that these tests are of prognostic value only when a series of observations is made which shows the trend of the changed function. A similar conclusion was made by Allen and Julian,¹⁸ who

10 Wilson, S. J. Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflections of Liver Damage in Humans, *Proc Soc Exper Biol & Med* **41** 559, 1939.

11 Quick, A. J. Conjugation of Benzoic Acid with Glycine. A Test of Liver Function. *Proc Soc Exper Biol & Med* **29** 1204, 1932.

12 Butt, H. R., Snell, A. M., and Osterberg, A. E. The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, *J A M A* **113** 383 (July 29) 1939.

13 Brinkhous, K. M., and Warner, E. D. Effect of Vitamin K on Hypoprothrombinemia of Experimental Liver Injury, *Proc Soc Exper Biol & Med* **44** 609, 1940.

14 Stewart, J. D., and Rourke, G. M. Prothrombin and Vitamin K Therapy. *New England J Med* **221** 403, 1939.

15 Rhoads, J. E. Physiologic Factors Regulating the Level of the Plasma Prothrombin. *Tr Am S A* **58** 86, 1940.

16 Lucia, S. P., and Aggeler, P. M. The Influence of Liver Damage on the Plasma Prothrombin Concentration and the Response to Vitamin K, *Am J M Sc* **201** 326, 1941.

17 Pohle, E. J., and Stewart, H. J. L. Observations on Plasma Prothrombin and Effect of Vitamin K in Patients with Liver or Biliary Tract Disease, *J Clin Investigation* **19** 365, 1940.

18 Allen, J. G., and Julian, O. C. Prothrombin and Hepatic Function, *Arch Surg* **45** 691 (Nov) 1942.

19 Andrus, W. Newer Knowledge of Vitamin K, *Bull New York Acad Med* **17** 116, 1941.

20 Andrus, W. DeW., Lord, J. W., Jr., and Moore, R. A. Effect of Hepatectomy on the Plasma Prothrombin and the Utilization of Vitamin K. *Surgery* **6** 899, 1939.

21 Warner, E. D., Brinkhous, K. M., and Smith, H. P. Quantitative Study on Blood Clotting. Prothrombin Fluctuations Under Experimental Conditions. *Am J Physiol* **114** 669, 1936.

22 Bollman, J. L., Butt, H. R., and Snell, A. M. Influence of Liver on Utilization of Vitamin K. *J A M A* **115** 1087 (Sept 28) 1940.

expressed the belief that the degree of prothrombin deficiency does not indicate the extent of the hepatic damage but that repeated observations reflect the clinical course of the hepatic disability

The prothrombin reaction to vitamin K is of service in distinguishing between the jaundice due to intrahepatic cellular injury or disease and that due to obstruction on the premise that in parenchymal disease of the liver vitamin K is not formed (Stewart²³, Stewart and Rourke¹⁴, Allen²⁴)

Andrus, Lord and Moore²⁰ have used the response of the plasma prothrombin level to menadione (2-methyl, 4-naphthoquinone) administered intramuscularly as a means of determining the site of origin of obstructive jaundice and obtained a high degree of accuracy. Thus it was correct in 32 of 36 cases of intrahepatic jaundice and in 49 of 50 cases of extrahepatic obstruction of the common duct, an over-all accuracy of 94 per cent. There were 20 additional cases of extrahepatic jaundice, not included in the aforementioned group, with an initial prothrombin level of over 80 per cent, a finding which when present in jaundice has always indicated it to be of extrahepatic origin.

The test is done as follows. Determinations of the level of plasma prothrombin are made on successive days by the Warner, Brinkhous and Smith²¹ test, until the levels are within 5 per cent of each other on two succeeding observations. Then 2 mg of menadione is injected intramuscularly, and the prothrombin is determined at intervals of twenty-four, forty-eight and seventy-two hours. It is usually not necessary to determine the prothrombin level for more than the successive days before injecting menadione.

PHYSIOLOGY OF THE PROTEINS

General Effect of Adequate Proteins—The quality and the quantity of dietary proteins influence growth, maintenance and repair as well as reproduction and lactation. In addition (like carbohydrate and fat) protein is an important source of energy. When much nitrogen is lost during fever, during an operation or following traumatic injury or other event proteins take part in the reparative processes in the body, and during convalescence adequate dietary proteins are required for the restoration of wasted tissues. For this purpose, according to Cuthbertson,²⁵ animal proteins seem more desirable than vegetable proteins.

Importance of Proteins in Antibody Formation—It has been shown experimentally (Breil and Haurowitz) that the protein stores of the body are of great importance in the formation of antibodies inasmuch as the antibodies of the rabbit were chemically identified with the globulin in normal rabbit serum except for the spatial arrangement of their constituent amino acids. In addition, the "antigenic template" (Cannon²⁶) seems to be synthesized from the intracellular protein reserves. These facts suggest the probable importance of a luxurious protein diet for the maintenance of adequate "antibody matrix" ("protein reserves") to serve as basic materials for the templation of specific antibodies. If so, the immunologic potential of the reticuloendothelial system, for example, would vary quantitatively with the amount of locally available protein reserve.

This suggested relationship is in line with statistical evidence covering the increased susceptibility to infectious diseases observed as a result of dietary insuff-

23 Stewart, J. D. Prothrombin Deficiency and Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, *Ann Surg* **109** 588, 1939.

24 Allen, J. G. The Diagnostic Value of Prothrombin Response to Vitamin K Therapy as a Means of Differentiating Between Intrahepatic and Obstructive Jaundice, *Internat Abstr Surg* **76** 401 1943, in *Surg, Gynec & Obst*, May 1943.

25 Cuthbertson, D. P. Quality and Quantity of Protein in Relation to Human Health and Disease, *Nutrition Abstr & Rev* **10** 1, 1940.

26 Cannon, P. R. Immunity and Protein Reserves. *New York State J Med* **43** 771, 1943.

iciency during World War I, and Cannon²⁶ was able to confirm this relationship on experimental animals. Rabbits whose protein reserves had been reduced by diets low in protein showed a distinctly subnormal capacity to produce specific antibodies.

The accumulated evidence in support of the relationship between protein reserves and specific immunity is of particular interest in view of the popular overemphasis of the role of vitamins in promoting antimicrobial resistance and the popular underestimate of the basic importance of a luxurious protein intake in association with the widespread custom of "dieting." Without more than enough protein to maintain nitrogenous equilibrium, antimicrobial vitamins are immunologically ineffective. "The reserve store of protein is the bulwark against infection" (Madden and Whipple²).

Typical of the observation bearing on this point is that of Clements,²⁷ who found that natives of the New Guinea region who eat a well balanced diet rich in proteins and vitamins are relatively immune to tropical ulcers, while other natives, who subsist on a less well balanced diet, in which the ratio of carbohydrate to protein is high and the supply of vitamins is poor, are susceptible. A complete absence of tropical ulcers was noted in fishing villages, where the diet contained 60 to 70 per cent of protein.

Protective Effect of Proteins on the Liver—(a) The protective effect of proteins against injury of the liver. The reserve proteins help to protect the liver against dietary, chemical, toxic or other injury. Experimental hepatic cirrhosis produced in rats by a low protein diet and prolonged administration of alcohol may be prevented by increasing the amount of total protein in the diet (Lillie, Daft and Sebrell²⁸, Gyorgy and Goldblatt,²⁹ and others).

Certain definite conclusions (Ravdin,³⁰ Whipple,³¹ and others) are now possible concerning the use of proteins and their activity in protecting the liver parenchyma against chemical poisons. Messinger and Hawkins³² found that a high protein diet (meat in the form of hamburger) was most effective in preventing hepatic injury from arsphenamine. Similarly, Goldschmidt and co-workers³³ and Davis and Whipple³⁴ demonstrated the marked action of protein foods (skimmed milk and casein) in protecting the liver against chloroform. Goldschmidt and co-workers³³ pointed out that protein in the liver has the following four modes of action: (1) probably some specific and as yet unknown action on the liver cell, (2) the action of displacing fat more effectively than carbohydrate, thereby making the liver less susceptible to injury, (3) an action through the fact that the liver is one of the chief storehouses of protein, and (4) the action of playing the major role

27 Clements, F. W. The Relation of Diet to Tropical Ulcer, *M. J. Australia* **1** 520, 1934 abstracted, *J. A. M. A.* **106** 139 (Jan 11) 1936.

28 Lillie, R. D., Daft, F. S., and Sebrell, W. H. Production and Apparent Prevention of a Dietary Liver Cirrhosis in Rats, *Proc. Soc. Exper. Biol. & Med.* **48** 228, 1941.

29 Gyorgy, P., and Goldblatt, H. Observations on the Conditions of Dietary Hepatic Injury (Necrosis, Cirrhosis) in Rats, *J. Exper. Med.* **75** 355, 1942, Choline as a Member of Vitamin B₂ Complex, *ibid.* **72** 1, 1940.

30 Ravdin, I. S., Stengel, A., Jr., and Prushnikin, M. The Control of Hypoproteinemia in Surgical Patients, *J. A. M. A.* **114** 107 (Jan 13) 1940.

31 Whipple, G. H. Blood Plasma Proteins, editorial, *Surg., Gynec. & Obst.* **73** 886 1941.

32 Messinger, W. I., and Hawkins, W. B. Arsphenamine Liver Injury Modified by Diet, *Am. J. M. Sc.* **199** 216, 1940.

33 Goldschmidt, S., Ravdin, I. S., and Lucke, B. Anesthesia and Liver Damage. The Protective Action of Oxygen Against Necrotizing Effect of Certain Anesthetics on the Liver, *J. Pharmacol. & Exper. Therap.* **59** 1 1937.

34 Davis, N. C., and Whipple, G. H. Influence of Drugs and Chemical Agents on the Liver Necrosis of Chloroform Anesthesia. *Arch. Int. Med.* **23** 636 (May) 1919.

in the regenerative phase, which begins within seventy-two hours after the original injury to the organ. Bollman and Mann³⁵ found a deleterious action of meat protein, but in their opinion this action is not due to the protein itself but to certain soluble extractives in the meat.

(b) The lipotropic function of protein. Protein undoubtedly has a specific effect in restricting intracellular deposition of fat as a result of the lipotropic activities of certain amino acids (Moise and Smith³⁶, Miller, Ross and Whipple³⁷, Goldschmidt, Vars and Ravdin³⁸, Messinger and Hawkins³², Perlman, Stillman and Chaikoff³⁹). In fatty livers these amino acids facilitate the mobilization of hepatic lipid and make it available for easy disposition. Lipocaine, choline and lecithin and the amino acids methionine and cysteine are active lipotropic agents, glycine, alanine, tyrosine, taurine, glutamic acid and proline have no lipotropic activity. Choline is thought to be necessary for the action of any lipotropic substance. This may account for the deterioration of hepatic function in patients with discharging biliary fistulas. It is significant that cysteine is a key amino acid for the regeneration of plasma protein also, while methionine is of no value in this process but is more important for its lipotropic activity.

In addition to the aforementioned factors, the significance of the total caloric content of the diet has been emphasized by Ravdin and his co-workers,³⁰ who found that a general diet high in calories was of greater value in lowering the lipid content of the liver than was the intravenous administration of dextrose alone.

(c) The mode of the protective effect of protein on the liver. It is believed that the amino acids methionine and cysteine are the agents responsible for the protective effect of the proteins (Miller, Ross and Whipple³⁷) by sparing the normal enzyme action of the oxidation-reduction activity in the hepatic cell, which is injured in chloroform poisoning. Since the milk protein, casein, is high in these amino acids, it seems likely that the specific effect of protein postulated by Goldschmidt and his co-workers³⁸ may rest on the same basis.

The exact mechanism whereby such hepatotoxic agents as chloroform and carbon tetrachloride exert their deleterious effects is not clear. The following hypothesis has been proposed. The toxic agents, having reached the liver, are held there in proportion to the amount of fat present, and exert their harmful effects by interfering with the normal oxidation-reduction system (anoxia) within the cells, involving glutathione and other factors. If the interference is sufficiently extensive, central lobular degeneration and necrosis follow.

Protection of the liver can be furthered and assured (1) by diminishing exposure to any toxic agent, (2) by feeding the patient a high caloric diet that is rich in protein and carbohydrate and low in fat, (3) by correcting any intracellular state of anoxia with cystine and methionine and with oxygen therapy, and (4) by giving an overabundance of protein to enhance the regenerative phase of liver activity. Additional protective mechanisms as yet not clearly understood may come later if

35 Bollman, J. L., and Mann, F. C. Influence of Liver in Formation and Destruction of Bile Salts, *Am J Physiol* **116** 214, 1936.

36 Moise, T. S., and Smith, A. H. Diet and Tissue Growth. I. The Regeneration of Liver Tissue on Various Adequate Diets, *J Exper Med* **40** 13, 1924.

37 Miller, L. I., Ross, J. F., and Whipple, G. H. Methionine and Cystine. Specific Protein Factors Preventing Chloroform Injury in Protein Depleted Dogs, *Am J M Sc* **200** 739, 1940.

38 Goldschmidt, S., Vars, H. M., and Ravdin, I. S. Influence of Foodstuffs upon Susceptibility of Liver to Injury by Chloroform and Probable Mechanism of Their Action, *J Clin Investigation* **18** 277, 1939.

39 Perlman, I., Stillman, N., and Chaikoff, I. L. Radioactive Phosphorus as Indicator of Phospholipid Metabolism. Further Observations on Effect of Amino-Acids in Phospholipid Activity of Liver, *J Biol Chem* **135** 359, 1940.

and when it is shown that substances such as choline, xanthine and some unknown factor of the B complex exert some specific action on the hepatic cell of which one is not as yet aware

CLINICAL HYPOPROTEINEMIA

During conditions of health and of illness the metabolic function of protein and its daily regulation depend on good function of the liver. It may be true that in many undernourished but otherwise apparently healthy persons and in many patients with latent or apparent parenchymal injury or disease of the liver the compensatory mechanism is sufficient to make good the ordinary wear and tear of the tissues and that there may be no laboratory or other method of determining that the protein reserves and hepatic function are actually deficient. On the appearance of any undue strain, however, such as illness, anesthesia or operation, this deficiency may become perceptible and is frequently demonstrable by laboratory means if it is not already apparent clinically. This fits in with the suggestion of Mann⁴⁰ that in doing tests for hepatic function the liver should be "strained" so as to bring out any abnormality. This was well illustrated in the following case.

CASE 2—A 39 year old man with polyposis of the colon underwent total colectomy in three stages. Prior to operation he was abnormally thin but was otherwise in fairly good general condition, and the plasma protein level was normal (7.52 Gm per hundred cubic centimeters at a specific gravity of 1.0294).

During the course of the convalescence and in between the stages of the colectomy were periods when the evacuations from the ileostomy were excessive. During these periods the patient lost progressively in weight, but several determinations of the plasma proteins showed normal results. However, during one episode when the amount of discharge from the ileostomy and the loss of weight were exceptionally severe, the blood serum protein dropped to an appreciably lower level, indicating the excessive strain being put on the protein metabolism and the protein replacement function.

Clinical Distribution of Hypoproteinemia—Various grades of hypoproteinemia have been clinically observed in many abnormal states and in many forms of disease. Deficiency of plasma protein, including lessening of the normal reserve, occurs in any basic condition of undernourishment (maintenance on an insufficient diet, starvation, prolonged vomiting), in any condition associated with loss of digestive capacity (disease of the stomach or of the pancreas, for example) and in any condition associated with decreased intestinal absorption with or without increased elimination from the alimentary tract (the various diarrheas and dysenteries).

Hypoproteinemic states are found in all varieties of disease of the liver, atrophic and hypertrophic cirrhosis, the various forms of acute and subacute yellow atrophy, biliary cholelithiasis, acute and chronic forms of cholangitis in its gross and capillary forms, and other conditions, after burns of the body, in syphilitic, tuberculous and cancerous disease of the liver, in all forms of traumatic toxic or chemical injury of the liver, and in the destruction accompanying suppuration of the liver (Johansen⁴¹, Thompson, McQuarrie and Bell⁴², Casten, Bodenheimer and Barcham,⁴³ and others).

In severe thyrotoxic disease two factors operate to produce protein deficiency: (1) an associated parenchymal lesion in the liver and (2) the increased catabolism

40 Mann, F. C. The Gastrointestinal Tract and the Liver. *J. A. M. A.* **121**: 720 (March 6) 1943.

41 Johansen, A. H. Hypoproteinemia, *Acta path et microbiol Scandina*. 1938 supp 37 p 272.

42 Thompson, W. H., McQuarrie, I., and Bell, E. T. Edema Associated with Hypogenesis of Serum Proteins and Atrophic Changes in the Liver with Studies on Water and Mineral Exchanges. *J. Pediatr.* **9**: 604, 1936.

43 Casten, D., Bodenheimer, M. and Barcham, I. A Study of Plasma Protein Variations in Surgical Patients. *Ann Surg.* **117**: 52, 1943.

of protein due to the generally increased metabolic activity shown by the high metabolic rate. The importance of this is becoming more and more generally known.

Protein deficiency also occurs in renal conditions (nephroses) in which albuminuria is an important factor. In certain severe conditions accompanied by excessive loss of nitrogen due to abnormal destruction of tissue, there are large losses of nitrogen in the urinary output, and tissue and reserve stores of protein become abnormally depleted. Frequently, too, this loss is enhanced by the inability to take and absorb nutrition for replacement purposes. Protein deficiency is also found in the malnutrition accompanying the wasting of any chronic disease (cancer, tuberculosis), often in association with various grades of anemia.

In accordance with the basic production mechanisms of hypoproteinemia, one can distinguish three types of this general protein deficiency.

(a) Hypoproteinemia of the prehepatic type is caused by interference with adequate nutritional intake, digestion or absorption of plasma protein-building materials without any disturbance of the ability of the liver to form plasma proteins, only the supply of protein building material is inadequate. This is the most general and important cause of hypoproteinemia.

CASE 3—A 60 year old woman was admitted to the hospital with the diagnosis of colonic cancer. A thorough workout failed to confirm the diagnosis. There was an enormous accumulation of intestinal content, and it took almost a week to clean out the colon thoroughly. There was so little desire for food for a number of weeks that the patient ate almost nothing. The total plasma protein was low—4.76 Gm per hundred cubic centimeters at a specific gravity of 1.0214. Several weeks after leaving the hospital the patient died, and although the actual cause of death was not established by postmortem examination, there is little doubt but that the continued extreme undernourishment was the important contributory factor.

(b) Hypoproteinemia of the hepatic type results from an inability of the liver itself to build plasma proteins despite the fact that adequate supplies of plasma protein-building material are received. In most of the reported cases, this is accompanied with other evidences of a reduction of hepatic function in the presence of apparent disease of the liver. A similar effect is demonstrable in latent hepatic disease also.

CASE 4—During the course of a cholecystectomy for attacks of gallbladder colic caused by small biliary calculi, it was demonstrated that several large glands were present at the porta hepatis, which surrounded the hepatic duct. At this time no jaundice was present, and the total serum protein was 6.39 Gm per hundred cubic centimeters. Later jaundice developed and became intense (icteric index, 108). Nothing could be done surgically to relieve the obstruction, which was proved to be due to these enlarged glands. When the patient died, the postmortem examination showed, in addition, biliary cirrhosis with accompanying splenomegaly. At the height of the jaundice the total plasma protein had declined to 5.0 Gm per hundred cubic centimeters.

(c) Posthepatic hypoproteinemia is caused by an abnormal loss of plasma proteins after adequate formation of these proteins by the liver as in (a) repeated bouts of severe diarrhea, (b) excessive albuminuria (nephrosis), (c) large hemorrhage, (d) any outpouring of serum into any hollow cavity (pleural effusion, peritoneal fluid in ascites or peritonitis), (e) exudation in large traumatic areas (burns). This form is often combined with undernutrition (group 1).

CASE 5—A 40 year old man with terminal ileitis suffered frequent bouts of fairly severe diarrhea combined with some ill-advised undernutrition. The total plasma protein was 4.6 Gm per hundred cubic centimeters in the presence of a continuous slight loss of weight.

General Pathologic Changes Due to Hypoproteinemia—(a) Nutritional edema In any appreciable hypoproteinemic state the most obvious alterations of tissue structure are those resulting from the disturbance in water distribution, namely edema of the subcutaneous tissues and of various viscera (more frequently the lungs and the gastrointestinal wall, less frequently the cardiac muscle, the liver, the pancreas, the brain and the skeletal muscle) Collections of fluid may also be found in the peritoneal, the pleural and the pericardial cavity There is no temporal or other correlation between the presence and the localization of the edema because the time of onset and the distribution of the edema are determined by (1) the intake of fluid, (2) the amount of basic ions, particularly sodium ions, dissolved in the body fluids (an increase in the amount of such ions tends to promote edema), (3) any increased permeability of the capillaries resulting from local burns or trauma, or general capillary injury (infection) (4) diminution of tissue tension or pressure (usually from any form of malnutrition)

In the absence of much deficit of tissue protein there is a greater tendency toward accumulation of fluid in the hollow spaces (e g, hydrothorax) With nutritional depletion of both plasma and tissue protein, a high incidence of subcutaneous edema occurs

When animals are fed low protein diets, the so-called nutritional edema develops presumably because there is a concomitant fall in the plasma protein level and in the osmotic pressure when the protein content of the diets is decreased In man, however, nutritional edema is often associated with other dietary deficiencies, even though the primary etiologic factor may be a diet insufficient to preserve nitrogen equilibrium The experimental evidence of this is still not conclusive Bloomfield⁴⁴ expressed the belief that other factors are present

(b) Defects in protein tissue Lesions of the tissues other than those associated with edema commonly take the form of defects in protein tissue—partial disappearance of the cardiac muscle fibers and of the muscle, fatty metamorphosis of the hepatic lobules with areas of necrosis in the midzonal areas (Bablet and Normet⁴⁵) loss of substance and increased water content of the hepatic cell (Elman and Heifetz⁴⁶)

Effect of Hypoproteinemia on the Liver—The effect of hypoproteinemic states on the liver cell is most definite In order to maintain a state of high efficiency in the liver cell abundant protein is necessary In hypoproteinemia, the lipotropic effect of protein is diminished, and the livers become fatty owing to the accumulation of fat in the hepatic cells In far advanced cases interstitial fibrosis (cirrhosis) follows

Experimentally, Gyorgy and Goldblatt²³ have shown that rats maintained on a diet low in casein with a moderately high content of fat and without choline regularly exhibited hepatic injury after between one hundred and one hundred and fifty days The hepatic injury exhibited in sequence changes that varied from diffuse necrosis, resembling human acute or subacute yellow atrophy, to advanced portal cirrhosis Diffuse necrotizing nephrosis was a frequent accompaniment of the hepatic injury (hepatorenal syndrome)

A certain amount of confusion has resulted experimentally because of reports of the possible deleterious effect on the kidney of diets rich in protein However, the results obtained by various research workers are conflicting, in some instances chronic nephritis was observed and

44 Bloomfield, A I The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat, *J Exper Med* **57** 705 1933, Effect of Carrot Feeding on Serum Protein Concentration of Rat, *ibid* **59** 687, 1934

45 Bablet I, and Normet L Les lésions histopathologiques de la bouffissure d'homme *Bull Acad de med, Paris* **117** 242, 1937

46 Elman, R, and Heifetz, C I Experimental Hypoalbuminemia Its Effect on Morphology, Function and Protein and Water Content of Liver I *Exper Med* **73** 417 1941

of protein due to the generally increased metabolic activity shown by the high metabolic rate. The importance of this is becoming more and more generally known.

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CASE 3—A 60 year old woman was admitted to the hospital with the diagnosis of colonic cancer. A thorough workout failed to confirm the diagnosis. There was an enormous accumulation of intestinal content, and it took almost a week to clean out the colon thoroughly. There was so little desire for food for a number of weeks that the patient ate almost nothing. The total plasma protein was low—476 Gm per hundred cubic centimeters at a specific gravity of 1.0214. Several weeks after leaving the hospital the patient died, and although the actual cause of death was not established by postmortem examination, there is little doubt but that the continued extreme undernourishment was the important contributory factor.

(b) Hypoproteinemia of the hepatic type results from an inability of the liver itself to build plasma proteins despite the fact that adequate supplies of plasma protein-building material are received. In most of the reported cases, this is accompanied with other evidences of a reduction of hepatic function in the presence of apparent disease of the liver. A similar effect is demonstrable in latent hepatic disease also.

CASE 4—During the course of a cholecystectomy for attacks of gallbladder colic caused by small biliary calculi, it was demonstrated that several large glands were present at the porta hepatis, which surrounded the hepatic duct. At this time no jaundice was present, and the total serum protein was 639 Gm per hundred cubic centimeters. Later jaundice developed and became intense (icteric index, 108). Nothing could be done surgically to relieve the obstruction, which was proved to be due to these enlarged glands. When the patient died, the postmortem examination showed, in addition, biliary cirrhosis with accompanying splenomegaly. At the height of the jaundice the total plasma protein had declined to 50 Gm per hundred cubic centimeters.

(c) Posthepatic hypoproteinemia is caused by an abnormal loss of plasma proteins after adequate formation of these proteins by the liver as in (a) repeated bouts of severe diarrhea, (b) excessive albuminuria (nephrosis), (c) large hemorrhage, (d) any outpouring of serum into any hollow cavity (pleural effusion, peritoneal fluid in ascites or peritonitis), (e) exudation in large traumatic areas (burns). This form is often combined with undernutrition (group 1).

CASE 5—A 40 year old man with terminal ileitis suffered frequent bouts of fairly severe diarrhea combined with some ill-advised undernutrition. The total plasma protein was 46 Gm per hundred cubic centimeters in the presence of a continuous slight loss of weight.

General Pathologic Changes Due to Hypoproteinemia—(a) Nutritional edema In any appreciable hypoproteinemic state the most obvious alterations of tissue structure are those resulting from the disturbance in water distribution, namely, edema of the subcutaneous tissues and of various viscera (more frequently the lungs and the gastrointestinal wall, less frequently the cardiac muscle, the liver, the pancreas the brain and the skeletal muscle) Collections of fluid may also be found in the peritoneal the pleural and the pericardial cavity There is no temporal or other correlation between the presence and the localization of the edema because the time of onset and the distribution of the edema are determined by (1) the intake of fluid (2) the amount of basic ions, particularly sodium ions, dissolved in the body fluids (an increase in the amount of such ions tends to promote edema), (3) any increased permeability of the capillaries resulting from local burns or trauma, or general capillary injury (infection) (4) diminution of tissue tension or pressure (usually from any form of malnutrition)

In the absence of much deficit of tissue protein there is a greater tendency toward accumulation of fluid in the hollow spaces (e g, hydrothorax) With nutritional depletion of both plasma and tissue protein, a high incidence of subcutaneous edema occurs

When animals are fed low protein diets, the so-called nutritional edema develops presumably because there is a concomitant fall in the plasma protein level and in the osmotic pressure when the protein content of the diets is decreased In man, however, nutritional edema is often associated with other dietary deficiencies, even though the primary etiologic factor may be a diet insufficient to preserve nitrogen equilibrium The experimental evidence of this is still not conclusive Bloomfield⁴⁴ expressed the belief that other factors are present

(b) Defects in protein tissue Lesions of the tissues other than those associated with edema commonly take the form of defects in protein tissue—partial disappearance of the cardiac muscle fibers and of the muscle, fatty metamorphosis of the hepatic lobules with areas of necrosis in the midzonal areas (Bablet and Normet⁴⁵) loss of substance and increased water content of the hepatic cell (Elman and Heifetz⁴⁶)

Effect of Hypoproteinemia on the Liver—The effect of hypoproteinemic states on the liver cell is most definite In order to maintain a state of high efficiency in the liver cell, abundant protein is necessary In hypoproteinemia, the hypotrophic effect of protein is diminished, and the livers become fatty owing to the accumulation of fat in the hepatic cells In far advanced cases interstitial fibrosis (cirrhosis) follows

Experimentally, Gyorgy and Goldblatt²⁹ have shown that rats maintained on a diet low in casein with a moderately high content of fat and without choline regularly exhibited hepatic injury after between one hundred and one hundred and fifty days The hepatic injury exhibited in sequence changes that varied from diffuse necrosis, resembling human acute or subacute yellow atrophy, to advanced portal cirrhosis Diffuse necrotizing nephrosis was a frequent accompaniment of the hepatic injury (hepatorenal syndrome)

A certain amount of confusion has resulted experimentally because of reports of the possible deleterious effect on the kidney of diets rich in protein However, the results obtained by various research workers are conflicting, in some instances chronic nephritis was observed and

44 Bloomfield, A L The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat, *J Exper Med* **57** 705 1933, Effect of Carrot Feeding on Serum Protein Concentration of Rat, *ibid* **59** 687, 1934

45 Bablet, J, and Normet, L Les lésions histopathologiques de la bouffissure d'Annam, *Bull Acad de med, Paris* **117** 242, 1937

46 Elman, R, and Heifetz, C J Experimental Hypoalbuminemia Its Effect on Morphology, Function and Protein and Water Content of Liver, *J Exper Med* **73** 417 1941

in others only apparently compensatory hypertrophy of the kidneys, without obvious lesions. The confusion has led to the conclusion of McCollum, Orent-Keiles and Day⁴⁷ that the "relation of dietary protein level to the kidney lesions remains a mystery." Observations on Eskimos in Greenland have shown that their high protein diet does not predispose to renal or to vascular disease. Stefansson and Anderson, who lived for a protracted period on an exclusive meat diet of high protein content, completed the experiment without rise in blood pressure or signs of renal impairment.

Effect of Hypoproteinemia on the Healing of Wounds—Clinically it is observed that hypoproteinemia is accompanied by difficulty in the healing of any coexisting operative wounds, owing to deficiency of fibroblast formation. Healing is slow, the tensile strength of the resultant scar is low and the tendency toward disruption of the wound is greater in this group than in patients with hyperproteinemia. The deleterious influence of hypoproteinemia seems to be limited to the proliferation of the fibroblasts.

In the case of colonic polyposis described on a foregoing page (case 2) it was noted that the condition of the wound about the ileostomy was exactly comparable to the state of nutrition and the level of protein in the blood plasma. In periods of protein deficiency the wound was covered with a grayish exudate and there was not only no evidence of progressive healing but the wound broke down additionally. As the state of nutrition and the level of protein in the blood plasma improved, these appearances disappeared, and one very successful and large transfusion of whole blood caused the wound to heal with extreme rapidity and with great efficiency.

Reversal of the Albumin-Globulin Ratio in Clinical Conditions—Foley and his associates⁴⁸ found that in the presence of advanced hepatic damage the albumin content of the blood plasma is reduced and there is a reversal of the albumin-globulin ratio. Snell corroborated this both clinically and experimentally and showed, in addition, that the findings become reversed as improvement takes place. According to Gray,⁴⁹ the most characteristic alterations of the plasma proteins are a large increase in gamma globulin and a decrease in plasma albumin. These changes are seen more frequently and to the greatest degree in cirrhosis of the liver and next most frequently in the acute parenchymal diseases. Frequently, the albumin-globulin ratio is normal, but chemical analysis shows that the qualitative distribution of the alpha, beta and gamma globulins is invariably abnormal during the acute stage. Significant increases in beta globulin are observed in all types of hepatic disease but to a considerably less degree and frequency than the globulin changes. Jaundice alone does not produce any significant changes in plasma protein. The diseased liver appears to produce the protein fractions of largest molecular weight. This may be explained by Whipple's⁵¹ theory that protein is stored in the liver as complex protein aggregates, which are broken down by the liver to supply plasma and tissue proteins as these are needed. This "intermediate protein" is converted into gamma globulin by the diseased liver more readily than into the smaller protein fractions, such as alpha globulin and albumin. It appears also that the protein changes associated with disease of the liver result primarily and to the greatest extent from the inability of the liver to produce normal plasma proteins rather than from external loss of proteins as in ascitic fluid.

47 McCollum, E. V., Orent-Keiles, E., and Dav, H. G. *Newer Knowledge of Nutrition*, New York, The Macmillan Company, 1939.

48 Foley, E. F., Keeton, R. W., Kendrick, A. B., and Darling, D. *Alterations in Serum Proteins as an Index of Liver Failure*, *Proc. Soc. Exper. Biol. & Med.* **33** 430, 1935.

49 Gray, S. J., in discussion on Greene, C. H. *Physiologic Considerations in Treatment of Portal Cirrhosis*, *J. A. M. A.* **121** 715 (March 6) 1943.

Postoperative Hypoproteinemia—A state of negative nitrogen balance exists for varying periods after operation. The important factors include (1) anesthesia, (2) a major surgical procedure with operative manipulation of deeply situated viscera and tissues, (3) a brief period of starvation, (4) shock fever, vomiting the presence of injured tissues and other abnormalities. Cuthbertson² demonstrated appreciable losses of nitrogen after severe injuries as well as after severe and extensive operations. There seemed to be no correlation between age, sex, or the presence or the absence of cancer or other type of disease and the extent of the loss of nitrogen.

The adverse effect of general and spinal anesthesia on the liver cell seems to be increased in hypoproteinemic states, preoperative and postoperative use of drugs of the sulfanilamide group also have the tendency to increase any destructive effect on the liver cell.

The major portion of the loss of protein occurs during the first four or five days after operation, during which time food is not permitted at all or only in limited quantities, ordinarily this seems to be the most important factor. Since this brief period of deprivation or limitation is well tolerated, the vast majority of the patients recover without any special attention to the temporary abnormality of the nitrogen balance and the hypoproteinemia is made good directly after the return to a full diet. However the diet must contain not only protein but also carbohydrate and fat as nitrogen equilibrium cannot ordinarily be achieved on a pure protein diet.

Postoperative Asthenia—Quite commonly it has been noted that following major surgical operations of various types there is frequently rather prolonged asthenia, which is often appreciable for a few weeks after discharge from the hospital. Leriche referred to this syndrome which cannot be clearly defined as *maladie postopératoire* and ascribed it to generalized disturbances of the sympathetic nervous system. This form of asthenia has been encountered, perhaps, most often after operation on the pancreas—pancreatic asthenia (Whipple³¹)—and less often after operation on the gallbladder or the liver, or after severe destructive disease. Not enough is known concerning all of these forms of postoperative asthenia, and further investigation is necessary. But it is interesting to speculate on the possible role of any postoperative loss of nitrogen in this connection. While the quantity of tissue protein lost may not be large, the source and the character of the catabolized protein under these conditions are not known and this protein conceivably differs from the stores depleted. General hypoproteinemia may result, or there may be a loss of certain reserve protein fractions or of necessary preceding amino acids, when in the course of their usual activities the subjects simply refrain from their customary protein foods and nevertheless continue their normal activities.

TREATMENT OF CLINICAL HYPOPROTEINEMIA

The preventive treatment of hypoproteinemic states depends to a great degree on the cause of the deficiency and on the method of its production. In ordinary states of undernourishment the essential of therapy is increased and abundant nourishment. In disease of the gastrointestinal tract, this must be combined with rectification of the underlying disease by an increase of the digestive action, by an elimination of abnormally increased bowel content and so on. In hemorrhage replacement of the lost blood is imperative. In essential disease or injury of the hepatic parenchyma, removal of the cause—chemical or other poisoning, deficiency of food with and without deficiency of vitamin supply and other causes—must be

accomplished In thyrotoxic disease, subtotal thyroidectomy is necessary In renal nephrosis and albuminuria the condition of the kidneys must be improved

In mild states of hypoproteinemia these measures, including the proper additional supply of protein foods by mouth, will suffice The oral administration of properly prepared amino acids is helpful It has been shown conclusively that a mixture containing all the essential amino acids can be administered orally without untoward effect, that amino acid mixtures so administered may be substituted for protein in the diet, that by this means a patient may be maintained in nitrogen equilibrium Amino acids are absorbed rapidly from the gastrointestinal tract Theoretically, essential amino acids introduced into the upper part of the jejunum should be promptly absorbed However, when introduced in large quantities in clinical practice they are apt to be irritating The two practical disadvantages at present are that the material is difficult to obtain in pure form and that it is expensive

If success does not follow in these cases of mild hypoproteinemia or follows in insufficient degree, or if the grade of the protein deficiency is severe, or if there is any necessity for urgency in the correction of the hypoproteinemic state more active measures are necessary, including the parenteral replacement of protein This has become an increasingly important clinical therapeutic need only during the past decade There is an increasing realization of the frequency and seriousness of hypoproteinemia in clinical conditions and of the apparent inability of the body always to correct this deficiency spontaneously There is a growing appreciation of the fact that protein needs other than those for the synthesis of plasma proteins are important in many patients nutritionally depleted and unable to absorb and utilize adequately nourishment by mouth Parenteral replacement of protein can be accomplished by (1) the transfusion of fresh whole blood, (2) the transfusion of wet or dried human plasma, (3) the reinfusion of ascitic fluid and (4) the parenteral administration of amino acids

Transfusion of Whole Blood or Plasma or Both—The transfusion of whole blood is the most satisfactory method for restoring the protein supply When for any reason blood is not available, human plasma forms a most excellent substitute and practically approaches completely fresh whole blood even though at present it suffers from the temporary disadvantages of expense and inadequacy of supply About 1,000 cc of plasma is required to raise the protein content of the plasma of the average adult 1 Gm per hundred cubic centimeters For severe hypoproteinemia many liters of plasma may be needed When plasma is given, absorption and synthesis are unnecessary After injuries of the liver or burns, for example plasma transfusions have proved life saving

Reinfusion of Ascitic Fluid—In the hypoproteinemia accompanying cirrhosis with ascites the patient's own ascitic fluid may be used Remarkable results have followed The plasma proteins become elevated, great diuresis follows, and the ascitic fluid may not reform for a rather long time

Parenteral Administration of Properly Prepared Amino Acids (for Example Hydrolyzed Casein)—The possibility of supplying protein parenterally with amino acids was successfully applied experimentally as early as 1913 by Henriques and Andersen⁵⁰ and has since been suggested for clinical use by others, particularly by Rose⁵¹ in 1934

⁵⁰ Henriques, V, and Andersen, A C Ueber parenterale Ernährung durch intravenöse Injektion, *Ztschr f physiol Chem* 88 357, 1913

⁵¹ Rose, W C The Significance of Amino-Acids in Nutrition, in *Harvey Lectures* 1934-1935, Baltimore, Williams & Wilkins Company, 1935, vol 30, p 49

(a) Administration by the intravenous route The intravenous administration of amino acids has been employed by Elman,⁵² Farr and MacFayden,⁵³ Shohl and associates,⁵⁴ Whipple and associates⁵⁵ and others Theoretically, the method is good, but it presents several practical difficulties, not the least of which is the preparation of a standardized hydrolysate safe for intravenous use The solution may be administered at the rate of 1 to 2 Gm of amino acid nitrogen an hour When so administered, over 95 per cent of the amino acids can be utilized in patients

The earlier difficulties have largely disappeared with successive improvements in the manufacture of proper hydrolyzed casein, which has been found to be the best source of material The solubility has increased so that a perfectly clear solution can be administered intravenously with a minimum danger of phlebitis when long periods of venoclysis are required This tendency, however, in any case is not great with the dilute (2 per cent) solutions

The most serious difficulty has proved to be the occurrence of occasional febrile reactions (Shohl and co-workers⁵⁴, Elman,⁵² and others)

Untoward reactions are due to one or more factors connected either with the manufacture of the hydrolyzed casein, with its method of solution and preparation for intravenous use or with the technique—the rapidity of the administration itself Whether such uniformity can be or actually has been achieved awaits further experience Nevertheless, the preparation now available for experimental use has been administered to 35 patients by Elman⁵²

In the experience of Brunschwig, Clark and Corbin⁵⁶ minor disturbances were frequent, including anoxia, mild and occasionally severe nausea and vomiting and a generalized disagreeable flushing sensation In exceptional instances these were sufficiently pronounced to warrant discontinuation of injections after one or several attempts

It appears that in certain types of acute hepatitis a sudden flooding of the circulation with amino acids is too great a physiologic load for the liver to tolerate Nevertheless, postmortem studies of 9 patients who received substantial quantities of casein digest during their terminal disease failed to reveal evidence of toxic effects ascribable to the digest

(b) Administration by the subcutaneous route When intravenous injections are not well tolerated, a 3.3 per cent solution in distilled water may be given safely by hypodermoclysis without discomfort and without reaction in the tissues Patients with clinical icterus or icteric forms with marked damage of the liver as shown by functional tests commonly have reactions after intravenous injections but tolerate hypodermoclyses of the 3.3 per cent solution well

⁵² Elman, R Parenteral Replacement of Protein with the Amino-Acids of Hydrolyzed Casein, *Ann Surg* **112** 594, 1940, Serum Albumin Regeneration Following Intravenous Amino-Acids (Hydrolyzed Casein) in Hypoproteinemia Produced by Severe Hemorrhage, *Proc Soc Exper Biol & Med* **43** 14, 1940

⁵³ Farr, L E, and MacFayden, D A Amino-Acid Nitrogen in Urine of Children with Nephrotic Syndrome Following Intravenous Amino-Acids, *Proc Soc Exper Biol & Med* **42** 444, 1939

⁵⁴ Shohl, A F, Butler, A M, Blackfan, K D, and MacLachlan, E Nitrogen Metabolism During Oral and Parenteral Administration of the Amino-Acids of Hydrolyzed Casein, *J Pediat* **15** 469, 1939

⁵⁵ Whipple, G H, Smith, H P, and Belt, A E Shock as a Manifestation of Tissue Injury Following Rapid Plasma Protein Depletion The Stabilizing Value of Plasma Proteins, *Am J Physiol* **52** 72, 1920

⁵⁶ Brunschwig, A, Clark, D E, and Corbin, N Postoperative Nitrogen Loss and Studies of Parenteral Nutrition by Means of Casein Digest *Ann Surg* **115** 1091, 1942

(c) Injection into the bone marrow Solutions of amino acids were found to be equally effective when injected into the bone marrow The latter method offers a satisfactory way of achieving parenteral administration when the other routes are inaccessible, impossible or inadvisable

SUMMARY AND CONCLUSIONS

A low concentration of plasma protein should be taken as a clinical indication of a profound nutritional disturbance and of a general metabolic deficiency disease This may be a primary condition or one secondary to serious disease especially of the hepatic parenchyma Any local manifestation may therefore be either the cause or the result of this abnormality, and commonly both of these effects become intertwined clinically Specifically, this has special reference to the albumin and globulin fractions of the total plasma protein in general cases of hypoproteinemia (undernutrition) and to the fibrinogen and prothrombin fractions in sharply defined activities relating to the blood-clotting materials and function

Diagnostic Value of Clinically Demonstrable Hypoproteinemic States—The importance of plasma proteins for clinical purposes lies in the fact that they can be measured In making the determinations, however, one must take account of any accompanying state of dehydration or of hemoconcentration, as these tend to give abnormally high values Plasma changes are clinically demonstrable only when the reserve supplies are sufficiently compromised In the latter event the protection afforded by abundant protein is lost

In clinical practice a single determination is not of much value A succession of observations is immensely valuable because it indicates the course of the illness—primarily in the deterioration or the improvement of the protein function and secondarily in the damage of the liver cells (see case 4)

In a general way the laboratory demonstration of a hypoproteinemic state with or without a coincident loss of body weight indicates some interference with the function of liver cells But inasmuch as the method of production of this deficiency varies there can be no assumption of intrinsic disease of the liver except as it corroborates one's diagnosis on other more appropriate and reliable criteria Nevertheless, even for this purpose the repeated determinations are valuable as corroborating proofs of damage of liver cells when all other clinical and laboratory findings point definitely to the liver as the essential seat of the disease, to a lesser extent, this is so when latent disease is suspected When repeated in a series, quantitative estimations of any protein deficiencies, with their progression or retrogression, give valuable information concerning the state of function of the parenchymal cells of the liver or of the deficiency in general and enable one to make fairly accurate prognostications So that when the deterioration of function is progressive, as indicated by the repeated tests, or when the grade of deficiency is extreme, the laboratory determinations act as important criteria for determining the advisability of any contemplated immediate operation, the choice of an anesthetic or the operative procedure In some cases they indicate efforts to improve the disabling factor, and operation must then be postponed until the disability is removed or sufficiently improved In still other cases they establish the irreversibility of the damage that has occurred, and when this is sufficiently far advanced, they contraindicate conclusively any operation of an elective nature

Several points have resulted from this study which seem to have a profound clinical importance In view of the present tendency to "diet" one should appreciate the fact that this may produce a state of undernutrition, protein deficiency and hypoproteinemia, the symptoms of which, perhaps little understood until now,

include (1) loss of weight and strength, (2) loss of stamina or energy, (3) various degrees of chronic fatigue and (4) much lessened resistance to disease. In many cases this latency predisposes to more profound changes, especially in the functions of the liver. And the prevalence of such latent conditions is little understood at its true clinical importance among members of the medical profession.

It seems to be true that the fat person is not necessarily "well nourished." In this type of person the available protein is usually relatively overshadowed by the fat content. A surgeon appreciates this because of his experience that such a patient is not a good subject for surgery.

The impression is growing that an enriched protein diet is not only advantageous but also necessary clinically for any one about to undergo the abnormal physical strain of an infection, an illness or an operation and for the prevention of any danger of postoperative hemorrhage. In this regard the previous clinical preference for a preponderating rich carbohydrate diet has suffered.

Similarly it seems that if at any time there arises the necessity for the administration of any drug which might have a toxic or otherwise deleterious action on the liver, one should supply a diet very rich in protein, which would have the tendency of forestalling such injury.

The Starling hypothesis has helped to explain many clinical conditions previously not so well understood. Sufficient available protein helps to maintain a normal colloidal osmotic pressure in the blood stream and in the capillary bed. Protein deficiencies are now thought to have important clinical bearings in the immediate postoperative period or after severe burns and injuries in that they bring about states of shock and collapse, in that they cause a more or less large reduction in the amount of urine excreted, in that they cause states of hemoconcentration and cause abdominal distention (Golden⁵⁷, Jones and Eaton⁵⁸, Leigh⁵⁹) and occasionally in that they facilitate obstructive manifestations (Ravdin and co-workers⁶⁰). Nutritional edema and the otherwise unexplained accumulation of fluid in the hollow spaces also are understood only on this basis.

The classification of states of hypoproteinemia into (1) acute (as after hemorrhage), (2) subacute (as after intestinal obstruction or peritonitis) and (3) chronic (as in chronic disease of the liver) is a more or less academic one. Clinically it suffices that one knows when and how these protein deficiency states occur and the measures available for their correction.

Effect of Therapy—Adequate knowledge of this kind has greatly enlarged the sphere of replacement and enrichment protein therapy as a protective effect for (1) preventing the deposition of fat in the liver cell, (2) preventing any impairment of the normal functions of the liver, (3) producing a powerful lipotropic activity when abnormal amounts of fat have previously been so deposited, (4) lessening the susceptibility to, and increasing the resistance to, toxic and chemical injuries, to infection and to other forms of disease, (5) treating some medical conditions (such as the different types of cirrhosis) in which protein deficiency is both a potential cause of the disease and an important consequence, (6) treating conditions (such as burns) in which there is a sudden depletion of protein stores, (7) facilitating reparative efforts after chemical or toxic injury of the hepatic parenchyma, (8) preparing patients better generally for any contemplated

57 Golden, R. Abnormalities of Small Intestine in Nutritional Disturbances. Some Observations on Their Physiologic Basis, *Radiology* 36 262, 1941.

58 Jones, C. M., and Eaton, F. B. Postoperative Nutritional Edema, *Arch. Surg.* 27 159 (July) 1933.

59 Leigh, O. C., Jr. Ileus Associated with Edema of Bowel, *Surg., Gynec. & Obst.* 75 279, 1942.

operation, (9) preventing potential specific dangers (such as postoperative hemorrhage), (10) lessening the injurious effect on the liver cells of drugs of the sulfanilamide group, (11) lessening the risk of general and spinal anesthesia, and (12) enhancing the efficiency of healing in operative and other types of wounds

Clinical Response of Hypoproteinemic States to Replacement Therapy—The response of any hypoproteinemia to replacement therapy will depend to a large extent on the mechanism of its production. In the hepatic type the severe damage of the liver renders the hypoproteinemia least responsive to treatment, and the response depends largely on the length of time the hypoproteinemia has been present and the amount of irreversible damage that has preceded treatment. The prehepatic type responds to treatment in proportion to the gravity of the cause. The posthepatic type of hypoproteinemia associated with burns usually responds rapidly to efficient early treatment.

The favorable effect of efficient treatment in clinical states of hypoproteinemia depends on (1) the ability to remove the underlying cause, (2) the ability to rectify any disturbance of hepatic function, (3) the relative shortness of time for which these two primary disabilities have been present and (4) the relative lack of pathologic anatomic changes, such as edema and tissue protein defects. Good and favorable results of efficient treatment cannot be expected when the aforementioned factors cannot be eliminated and when any degree of infection is present and cannot be controlled.

Unknown Factors—There seems to be a great necessity for the study of certain hitherto elusive factors which seemingly have a profound effect. Not always do the available methods of therapy and protein replacement bring about the desired results to one's clinical satisfaction. For instance, it frequently happens that transfusions of either plasma or whole blood are given and not much change is apparent, then a transfusion is given from another donor, and the result seems almost miraculous. It must be, therefore, that certain factors become available which were not present previously, provided through the agency of the new donor. One sees these effects clinically not infrequently.

12 East Eighth-Seventh Street

RECONSTRUCTIVE PLASTIC SURGERY OF THE ABSENT EAR WITH NECROCARTILAGE

AN ORIGINAL METHOD

EDWARD S LAMONT, M D

HOLLYWOOD, CALIF

The individuality of the ear cartilage, and its position away from the head, makes reconstruction of the absent ear one of the most complex of all plastic problems. One of the modern pioneers in the work, Updegraff, so aptly said that he like many others, including Blair, Brown, Gillies, New, Padgett, Kirkham and Pierce, had the same attitude toward their reconstructed ears as a girl has toward her legs "They're all right but I wish they were prettier"

HISTORICAL REVIEW

In the sixteenth century Tagliacozzi¹ devised a method to repair partial losses of the ear by utilizing skin flaps from the scalp and neck. von Szymanowski² in 1870 definitely outlined a technic for restoration of the auricle. He raised flaps around the scalp and mastoid region, folded the tissue on itself, sutured the margins and then grafted the resultant raw defect. In 1908 Schmieden,³ utilizing autogenous rib cartilage, implanted it in a flap on the breast, then transferred the flap containing the cartilage to the region of the auricle. In 1916 Joseph⁴ employed a pedicle flap from the upper aspect of the arm to reconstruct the absent ear. Later, in 1930, he implanted ivory in a raised flap on the neck, then turned the flap and attempted to create an auricle.

Gillies,⁵ in 1920, used the skin over the mastoid area, implanted autogenous rib cartilage, raised this flap containing the cartilage to form the ear, then grafted the defect on the posterior aspect with the aid of an Esser outlay. In 1928 Pierce⁶ made a perceptible step forward by utilizing a tube pedicle from the neck and draping it over the outer aspect of the reconstructed ear to simulate a helix, for the first time giving the ear reasonable size, contour and identity. In 1937 Gillies⁷ first suggested the use of maternal ear cartilage as framework for a new ear. Though it left the mother with some deformity, she was able to cover the robbed ear with hair, and the surgeon gained a total ear cartilage for transference to her offspring.

From the Division of Reconstructive Plastic Surgery, Cedars of Lebanon Hospital, Hollywood, Calif

Presented in abridged form at a sectional meeting of the Los Angeles County Medical Association April 1943, in conjunction with colored motion pictures

1 Tagliacozzi, G. *De curtorum chirurgia per insitionem*, libri duo, Ventus, apud G Bindonum jun, 1597

2 von Szymanowski, J. *Handbuch der operativen Chirurgie*, Braunschweig F Vieweg u Sohn, 1870

3 Schmieden, V. *Der plastische Ersatz von traumatischen Defekten der Ohrmuskel*, Berl klin Wchnschr 45 1433-1435, 1908

4 Joseph, J. *Korrektive Nasen und Ohrenplastik*, in Katz, L, Preysing, H, and Blumenfeld, F. *Handbuch der speziellen Chirurgie des Ohres*, Leipzig, Curt Kabitzsch, 1921

5 Gillies, H. *Plastic Surgery of the Face*, London, Oxford University Press, 1920

6 Pierce, G W. *Reconstruction of the External Ear*, Surg, Gynec & Obst 50 601-605 (March) 1930

7 Gillies, H. *Technique in Construction of Auricle*, Tr Am Acad Ophth (1941) 45 119-121 (Jan-Feb) 1942

Other Modifications—Many workers⁸ have devised modifications of known methods. Padgett⁹ has presented the use of a tube pedicle flap extending from the tip of the mastoid to the midclavicular region, he splits the tube, using the larger pedicle to cover the defect on the posterior aspect as well as to anchor the ear while he uses the smaller one over the ear to simulate a helix.

J. B. Brown¹⁰ suggested the use of alcohol-fixed homogenous cartilage for reconstructing the absent ear, however, it has been his policy of late to adhere to direct transplants with autogenous rib cartilage. Pierce and O'Connor¹¹ have projected a method of using preserved rib cartilage, refrigerated and stored in merthiolate saline solution, 1:1,000. Greeley,¹² following Gillies' method of using maternal ear cartilage, has outlined a procedure whereby a dental mold of the donor's (mother's) ear is applied after the cartilage has been removed. He believes that by this method of support excessive shrinkage is prevented. Updegraff¹³ suggested that preserved rib cartilage be utilized to replace the donor's ear and thus lessen the resulting deformity.

Kirkham¹⁴ removed cartilage from rabbits' ears in chronologic hours after their death. He transplanted the cartilage to live rabbits, then he examined it six months later. He reports that the cartilage had retained its dimension and form. Microscopically it was divulged that the cell spaces were vacuolated and the nuclei markedly deformed. He also suggests¹⁴ that ear cartilage of cadavers might be used for reconstructing the absent ear.

Converse, discussing Gillies'⁷ paper in 1941, presented a motion picture film depicting transplantation of ear cartilage taken from a donor who had died two hours previously from coronary thrombosis.

OTHER PROBLEMS ARISING WITH THE ABSENT EAR

The ear is partially or totally absent in approximately 1 out of 20,000 infants at birth. The parents immediately assume guilt, and it requires careful tact on the part of the physician to explain these congenital deformities. The reconstruction of the absent auricle may physiologically be begun when the patient is 5 or 6 years old, as at this time the ears have virtually gained their full normal growth. However, in a great majority of cases some procedure must be started earlier to appease the parents and to cushion their psychic upset.

Presurgical Procedures—When babies with a remnant of an ear like the ear in figure 1 are presented for reconstruction, we insert either a vitallium metal mold

8 Cox, G. H. Surgery of the Auricle, Laryngoscope **51** 791-797 (Aug.) 1941. Davis, A. D. Plastic Surgery of the Ear, Nose and Face, Arch Otolaryng **10** 575-584 (Dec.) 1929. New, G. B. Reconstruction of External Ear, Proc Staff Meet, Mayo Clin **6** 97 (Feb. 18) 1931.

9 Padgett, E. C. Total Reconstruction of the Auricle, Surg, Gynec & Obst **67** 761-768 (Dec.) 1938.

10 Brown, J. B. Preserved and Fresh Homotransplants, Surg, Gynec & Obst **70** 1079-1082 (June) 1940.

11 O'Connor, G. B., and Pierce, G. W. Refrigerated Cartilage Isografts, Surg, Gynec & Obst **67** 796-798 (Dec.) 1938. O'Connor, G. B. Merthiolate (Mercury Compound) Tissue Preservative and Antiseptic (for Refrigerated Cartilage Isografts), Am J Surg **45** 563-565 (Sept.) 1939, Refrigerated Isografts: Source, Storage and Use, California & West Med **52** 21-23 (Jan.) 1940.

12 Greeley, P. W. Reconstruction Otoplasty, Surgery **10** 457-461 (Sept.) 1941.

13 Updegraff, H. L. The Cartilage Implant, Am J Surg **14** 492-498 (Nov.) 1931, Reparative Surgery, Australian & New Zealand J Surg **9** 237-258 (Jan.) 1940.

14 Kirkham, H. L. D. Use of Preserved Cartilage in Ear Reconstruction, Ann Surg **111** 896-902 (Mar.) 1940.

or preserved rib cartilage so as to stretch the skin. Thus we gain sufficient skin to act as a recipient for the ear necrocartilage which is implanted when the child has reached the age desirable for its acceptance.

External Auditory Canal—The problem of creating an external auditory canal often arises. It is localized to congenitally absent ears unless the ear has been traumatically evulsed. Before an attempt is made to reconstruct a canal the following measures must be carried out. Careful audiograms are taken to evaluate hearing on the affected side and to gauge the amount of possible improvement that might occur if a canal were present. Laminograms of the middle ear should be made, to substantiate the presence of ossicles. It has been the experience of my associates and myself that patients with a congenitally absent ear have some defect of the inner ear. The hearing of many of these patients with no canal is decreased from 20 to 50 decibels and drops off more for the high tones. The latter fact might serve to substantiate that the loss is perceptive rather than conductive, in which case hearing would be less for all tones. Beck¹⁵ in performing an autopsy on a patient with a rudimentary ear found an absence of the middle and the inner ear. There are several such cases reported in the literature, substantiating our clinical findings.

Method of Reconstructing the External Auditory Canal—Should the canal require construction the method of procedure is briefly as follows. The area for the future canal is carefully dissected, and its diameter calibrated to allow appreciably for shrinkage. A split skin graft is sutured around a dental stent with the skin surface inward. This mold is inserted into the previously dissected area and allowed to remain until the graft has been accepted.

As a rule the external auditory canal is not necessary for cosmetic effect, and its ability to improve hearing in these cases is rare.

Facial Atrophy—In virtually 90 per cent of our cases of a congenitally absent ear there has been facial asymmetry on the affected side. Measurements demonstrate that side of the face to be smaller, and examination reveals the musculature to be underdeveloped. It might be logical to believe that the congenital lesion affecting the facial nerve somewhere along the canal also involves the inner structure of the ear.

PURPOSE OF THE EXPERIMENT

A review of ears reconstructed by most methods revealed that many presented mutual disadvantages. Some were too small when compared with the opposite ear. The general contour was often too gross and did not present the delicate whorls indigenous to ear cartilage. Many had collapsed into bizarre shapes because the struts of rib cartilage were insufficient as framework. In others the skin graft placed over the defect on the posterior mastoid surface had contracted or its pigment had been affected so as to be cosmetically unattractive. In a few cases the incision was cut too high on the scalp and included an area with hair which continued to grow on the anterior surface of the reconstructed ear, many in spite of epilative procedures.

With these factors in mind we sought a new method or some modification of an existing one that might improve the final result in reconstructed ears. Scientific procedures are much like a telephone dial. The few numbers are constant but their combinations are almost innumerable, and often the correct combination presents something interesting and choice on the other end of the line.

15 Beck, J. C. The Anatomy, Psychology, Diagnosis and Treatment of Congenital Malformation and Absence of the Ear, *Laryngoscope* 35 813-831 (Nov.) 1925

The purpose of the experiment was to decide the course of necrocartilage in human beings when placed in pockets in the abdominal wall, in the posterior mastoid area, and when kept in solution, then to compare these results with cartilage handled in the same way but primarily treated with different solutions and finally to compare necrocartilage with autogenous cartilage

EXPERIMENTAL METHOD

The total ear cartilage was dissected from a person after he no longer had any use for it I call this cartilage *ear necrocartilage* Further, sections of rib cartilage were taken from the same person for comparative study I call this cartilage *rib necrocartilage* The total ear cartilage taken was treated in several different ways Some cartilage was placed in solution of formaldehyde for four days, then carefully washed, transferred to merthiolate solution and stored in the ice box Other specimens were placed directly in the merthiolate solution and refrigerated

In patients chosen for an ear necrocartilage graft, pieces of the same graft were transplanted to pockets in the anterior abdominal wall In 1 case (fig 10) a piece of ear necrocartilage was placed in a prepared pocket, a section of normal ear cartilage taken from the opposite ear in another and a piece of rib necrocartilage in a third Portions of these three sections of cartilage were refrigerated in merthiolate saline solution At the end of seven days and again in forty-four, microscopic sections were made of all specimens and compared

PREVIOUS EXPERIMENTAL INVESTIGATION WITH CARTILAGE

Various materials have been used as framework for reconstruction in ears as well as in other parts of the body These include ivory, animal bone, paraffin celluloid, human bone, cartilage and more recently metals New¹⁶ reported the experimental transplantation of celluloid beneath the nasal skin in dogs, and in this specific series he used it clinically in 5 patients Though reporting reasonable success, he discarded its use in favor of autogenous bone and cartilage transplants

Aufricht¹⁷ reported the use of ivory intranasally in a series of 50 patients, and though he had no untoward results discontinued its use a dozen years ago in favor of autogenous transplants Salinger¹⁸ reported a series of 65 cases in which he used ivory for implantation, removal was necessary in 5 of these following surgical procedures, either because of infection or because of intolerance of the tissue to the foreign body

Murphy¹⁹ carried out extensive experimental work on the use of autogenous bone grafts He found that bone transplanted in the same person when contacted with bone becomes united and is used as a bridge for the reproduction of new bone Cohen¹⁷ has utilized this principle in intranasal bone and cartilage grafts

Cartilage more than any other element has been used experimentally as an implant Work has been carried out, both in animals and in human beings with living and dead cartilage Bert²⁰ in 1865 transplanted living cartilage to animals, then he examined it after the latter had been killed and concluded that the grafts retained their viability and eventually calcified Prudden²¹ in 1881 implanted

16 New, G B The Use of Celluloid in Correction of Nasal Deformities, J A M A 70 988-990 (April 6) 1918

17 Aufricht, quoted by Cohen, L Advantage of Mixed Bone and Cartilage Grafts in Correction of Saddle Nose and Other Depressed Deformities of Dorsum, Ann Otol, Rhin & Laryng 49 410-417 (June) 1940

18 Salinger, S Saddle Nose A Report on the Use of Ivory and Cartilage Implants Illinois M J 72 412-417 (Nov) 1937

19 Murphy, J B Osteoplasty, Surg, Gynec & Obst 16 493-536 (May) 1913

20 Bert, P Sur la greffe animale Compt rend Acad d sc 61 587, 1865

21 Prudden, T M Experimental Studies on the Transplantation of Cartilage Am J M Sc 82 360-370, 1881



Fig 1—*A*, complete absence of right ear depicting lack of cartilaginous structure and malformation of the vestigial auricle. In many such cases the tissue present may be utilized and stretched with vitalium mold or necrocartilage ear. Often the vestigial structure must be discarded and the total ear reconstructed. Frequently the external auditory canal is absent and little hearing is present, owing to defects in the inner ear. Careful planning of all stages in the procedure must be done at this time.

B, struts made of autogenous rib cartilage have been inserted to enlarge the ear, give it framework and create contour. A sternomastoid tube pedicle has been raised and later will be severed and the distal end waltzed upward.

C, the tube pedicle has been waltzed up to position. It has been fashioned to the desired length and width, so that it does not kink and is cosmetically attractive.

D, more autogenous cartilage has been inserted into the interstices of the auricular tissue so as to create an ear approximately the same size and shape as the unaffected one. The pedicle has been waltzed to the anterior surface of the new helix so as to be in appropriate position.

E, the tube pedicle has been attached and draped, thus giving it size, shape and similarity to the opposite ear.

F, the ear has now been fashioned to the desired shape and though it may not have all the intricate whorls indigenous to a normal ear, it closely resembles the opposite ear and is cosmetically satisfactory. (Case of the late Howard L. Updegraff.)

cartilage preserved in 95 per cent alcohol and found that partial absorption and degeneration occurred in all these grafts Olher²² in 1867, substantiated later by Zahn's²³ work in 1884, found that both autogenous and homogenous cartilage grafts in animals presented degenerative changes with subsequent absorption of the material regardless of the type of grafts Fischer²⁴ in 1882 after experimental work with animals concluded that removal of the perichondrium was the primary cause of degeneration and absorption of cartilage grafts, whereas retention of it caused the cartilage to remain intact In 1889 von Mangoldt²⁵ reported a series

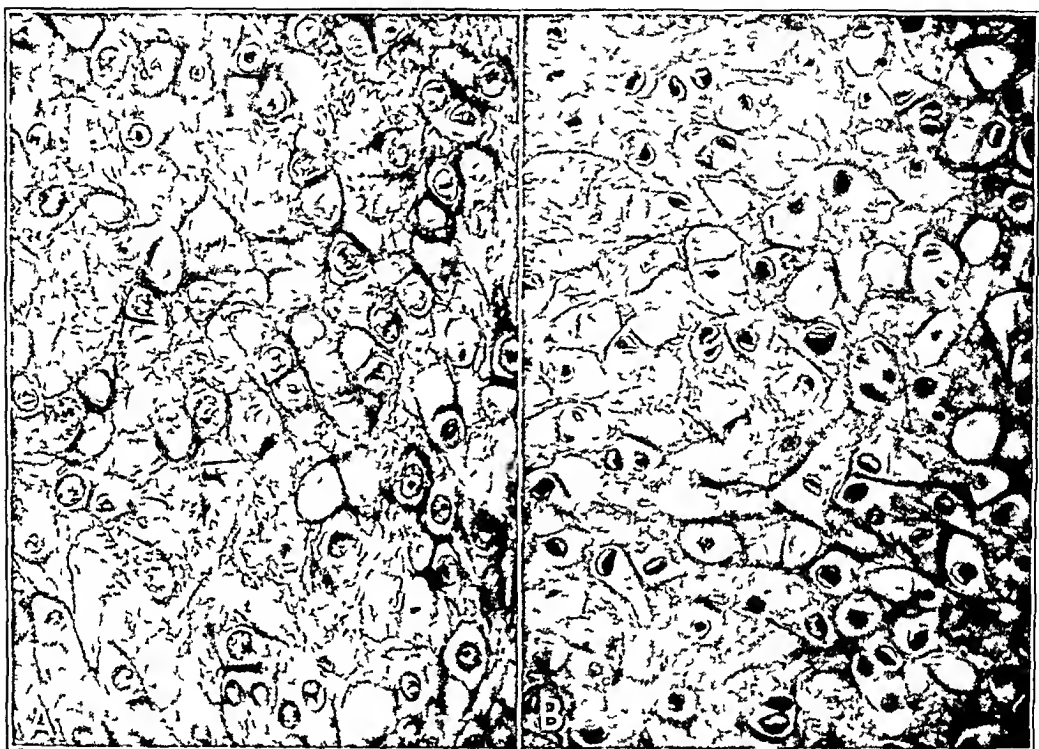


Fig 2—A, ear necrocartilage preserved in solution of formaldehyde four days, refrigerated in merthiolate-saline solution eighteen days and then implanted in the abdominal wall for ninety-six days Section reveals considerable scar tissue around the plate of cartilage In the scar tissue can be seen a pronounced foreign body granulomatous inflammation The plate of cartilage shows moderate dissolution of the cells at the periphery with only phantoms of the former structures remaining Toward the center the cells are better preserved, many are vacuolated but in places intact nuclei are visible The matrix is uniformly pink with slight granularity, chiefly around the cells $\times 165$

B, ear necrocartilage preserved in solution of formaldehyde four days, then refrigerated in merthiolate-saline solution for one hundred and fourteen days Section of this tissue shows in sharp contrast to the preceding one extremely well preserved cartilage with prominent nuclei and cellular outlines In places the matrix is stained pink and in others lavender The perichondrium is not remarkable $\times 183$

22 Olher, L Traite experimental et clinique de la regeneration des os et de la production artificielle du tissu osseux, Paris, V Masson & fils, 1867

23 Zahn, F W Ueber das Schicksal der in den Organismus implantirten Gewebe, Virchows Arch f path Anat 95 369-387, 1884

24 Fischer, E Ueber Transplantationen von organischem Material, Deutsche Ztschr f Chir 17 362, 1882

25 von Mangoldt F Arch i klin Chir 39 926, 1889

of cases in which he successfully transplanted autogenous costal cartilage to the bridge of the nose in human beings. Nelaton and Ombredanne²⁶ implanted autogenous costal cartilage in a forehead flap and subsequently utilized the pedicle in reconstructing an absent nose.

In 1926 Loeb,²⁷ using hyphoid cartilage with perichondrium both as autogenous and homogenous grafts in guinea pigs, examined the cartilage microscopically in chronologic order from a day to five and one-half months later. Though the grafts were successful, he found virtually no reaction around the autografts and a concentration of lymphocytes and connective tissue around the homografts with necrosis of the latter. Interestingly enough in the latter graft, local reaction disappeared

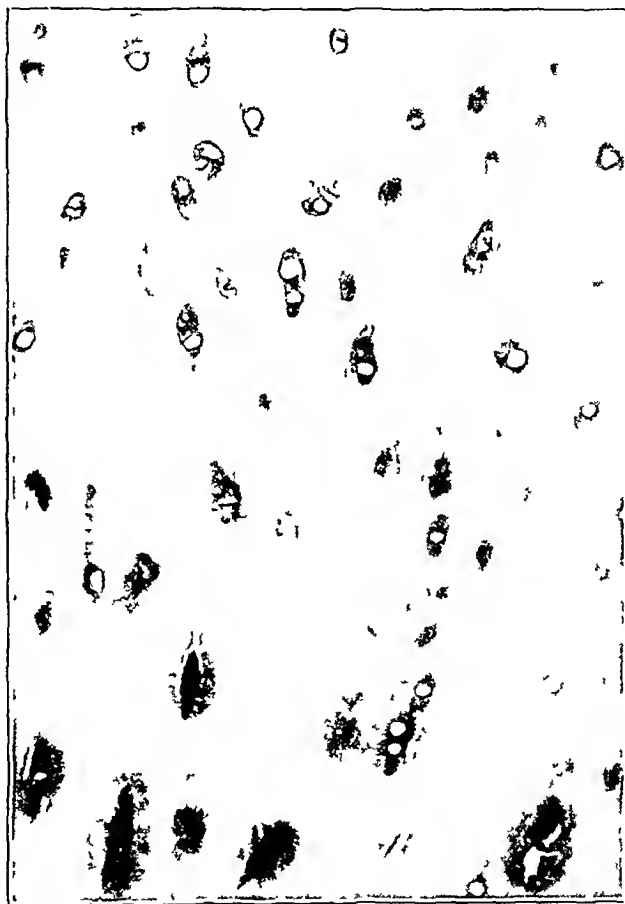


Fig 3—Fresh rib cartilage specimen taken from a patient at the operating table and refrigerated in merthiolate-saline solution for ninety-six days. Section of this tissue reveals a fairly well preserved structure. The matrix is uniformly hyaline. Immediately around the cells the matrix is deeply blue stained. Elsewhere it is bluish pink. The cells are considerably vacuolated for the most part. In some places they are well preserved with intact nuclear structures. $\times 220$

after three weeks, and when he removed the piece five and one-half months later, it was practically intact. In 1926 Mannheim and Zypkin,²⁸ implanting autogenous

²⁶ Nelaton, C, and Ombredanne, L. *La rhinoplastie*, Paris, G. Steinheil, 1904.

²⁷ Loeb, L. Autotransplantation and Homoiotransplantation of Cartilage in Guinea-Pig, *Am J Path* 2 111-122 (March) 1926.

²⁸ Mannheim, A, and Zypkin, B. Ueber freie autoplastische Knorpeltransplantation *Arch f Klin Chr* 141 668-672, 1926, abstracted, *J A M A* 87 2132 (Dec 18) 1926.

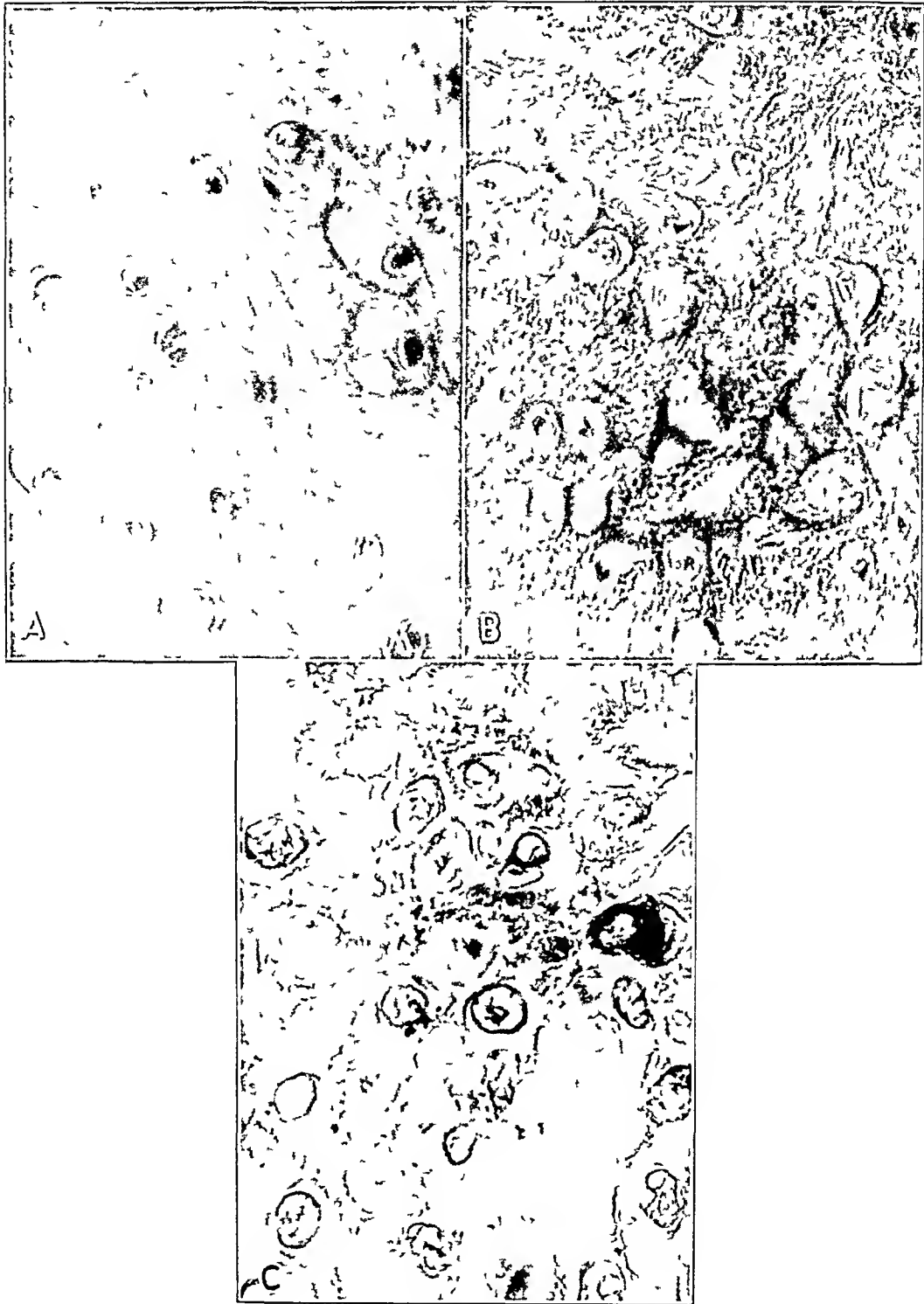


Figure 4

(See legend on opposite page)

cartilage in guinea pigs, noted that though the former retained all its structure, after a time there were small microscopic changes, both degenerative and regenerative. They concluded, further, that cartilage transplanted without perichondrium was better preserved than cartilage transplanted with perichondrium. Nageotte²⁹ in 1922, using rabbit ears as the recipient area, refrigerated cartilage previously fixed in alcohol. He reported that after a time the surrounding tissues invaded the cartilage, that the cartilage lost its staining properties, and that some calcification took place.

Davis³⁰ in 1917 used autogenous rib cartilage for intranasal transplants and concluded that there was little or no absorption. A similar view was reported by Gillies⁵ in 1920 and his clinical conclusions were that homografts were reasonably permanent and rarely invaded by fibrous tissue. He hoarded a piece of autogenous cartilage and a piece of fresh homocartilage in a pocket beneath the abdominal wall of a patient and after a year and one-half found both pieces viable with no change in the autograft and the homograft showing some vacuolation of cells.

In 1922 Poletti³¹ buried alcohol-fixed cartilage in various parts of rabbits and found fibroblastic and connective tissue penetration within the cartilage, associated with new cartilage and bone formation. In 1927 Nigrisoli³² took cartilage from a calf, fixed it in alcohol and grafted it in guinea pigs. He examined the grafts after a week and after six weeks, and though they had survived, fibroblastic and connective tissue invasion into the cartilage had occurred in conjunction with calcification.

Neuhoff³³ in 1923 used autogenous rib transplants in patients and concluded that they were eventually absorbed and replaced by fibrous tissue. Didier and

29 Nageotte, J. Organisation de la matière dans ses rapports avec la vie, Paris, Masson & Cie, 1922.

30 Davis, J. S. Some of the Problems of Plastic Surgery, *Ann Surg* 66 88-94, 1917.

31 Poletti, B. Su neoformazioni cartilaginee ed ossee determinate da innesti di frammenti di cartilagine e d'osso fissati, *Arch ital di chir* 6 179-191 (Nov) 1922.

32 Nigrisoli, P. Esperimenti di innesto di cartilagine fissata nel rene e di sostituzione di parti scheletriche con cartilagine fissata, *Arch per le sc med* 49 689-703 (Dec) 1927.

33 Neuhoff, H., and Hirschfeld, A. The Transplantation of Tissues, New York, D Appleton and Company, 1923, pp 205-215.

EXPLANATION OF FIGURE 4

A, fresh ear cartilage taken from a patient at the operating table and placed directly into Boun's solution to be used as control. The tissue is well preserved. Three sections reveal well preserved cartilage cells embedded in a hyaline matrix. The staining quality of the matrix varies slightly, some portions being pink, other portions having a slight lavender cast. In some places in the latter areas there is a fine granularity to the matrix. The cartilage cells are slightly shrunken, but the nuclei are visible. A few cartilage cells can be seen without evidence of nuclei. $\times 183$

B, fresh ear cartilage implanted in the anterior abdominal wall for seven days. Section reveals a small amount of organizing granulation tissue around the periphery. The cartilage presents moderate alteration from the normal. There appears to be a dissolution of the matrix characterized by an irregular mottling of portions of the matrix with pink while the remainder is light and dark blue. The cartilage cells show loss of nuclei with considerable vacuolation of the cells to a large extent. $\times 183$

C, fresh ear cartilage implanted in the anterior abdominal wall for forty-four days. The piece of cartilage shows considerable dissolution of the usual architecture with only phantoms of the former structures remaining. The matrix is diffusely pink. The outlines of the former cells and nuclei can be seen in some areas. The remainder of the tissue shows considerable fibrosis. $\times 183$



Figure 5

(See legend on opposite page)

Guyon³⁴ in 1928 utilizing rabbits as recipients implanted alcohol-fixed cartilage grafts. After eight and one-half months microscopic sections revealed fibroblastic invasion and calcification of the cartilage.

In 1938 Peer³⁵ implanted sections of human septal and costal cartilage, preserved in 50 per cent alcohol, beneath the skin of the anterior thoracic wall of human beings. The transplants were removed for microscopic examination at chronologic intervals from one week to fourteen months. He found a foreign body reaction about the transplants which lasted until the thirty-second day and was virtually absent in sections removed later. From the thirty-second day through four months the graft remained as a tolerated dead foreign body. The cartilage buried for fourteen months disclosed fibroblastic invasion with some absorption and calcification. In 1939 Peer³⁶ reported further on this work. He said that dead cartilage grafts fixed in alcohol and buried under the skin of the chest of human beings and examined after nine and one-half months to two years showed a progressive invasion by fibroblastic tissue and partial absorption of the cartilage, whereas autogenous rib cartilage hoarded under the same circumstances and at the same time showed no invasion or absorption. Two pieces of autogenous cartilage buried for four and one-half and six years respectively appeared microscopically as living cartilage. He concluded that fresh autogenous rib cartilage was better material for plastic repair than autogenous cartilage fixed in alcohol.

Brown³⁷ after years of experience with homografts is rational in his conclusions. He presents the obvious advantages of homogenous cartilage. It is

34 Didier, R., and Guyon, L. Production de cartilage et d'os, au sein de greffes vivantes et mortes, chez le lapin, *Compt rend Soc de biol* 98 443-445 (Feb 17) 1928.

35 Peer, L. A. Cartilage Transplanted Beneath Skin of Chest in Man. Experimental Studies with Sections of Cartilage Preserved in Alcohol and Buried from Seven Days to Fourteen Months, *Arch Otolaryng* 27 42-58 (Jan) 1938.

36 Peer, L. A. Fate of Living and Dead Cartilage Transplanted in Humans, *Surg, Gynec & Obst* 68 603-610 (March) 1939.

37 Brown, J. B., and McDowell, F. Skin Grafting of Burns, Philadelphia, J. B. Lippincott Company, 1943. Brown¹⁰

EXPLANATION OF FIGURE 5

A, specimen of ear necrocartilage taken and placed directly in Boun's solution for fixation. The cartilage presents a mottled appearance with multiple focal areas of necrosis. In the latter areas the outlines of the structures are considerably obliterated. Elsewhere the matrix is a mottled light and deep pink. The cells which are somewhat shrunken in some places show lysis. Elsewhere though somewhat shrunken the nuclei are darkly stained and well preserved. $\times 183$

B, ear necrocartilage implanted in the anterior abdominal wall for seven days. This tissue in comparison with the preceding is better preserved. There is similar irregular mottling of the matrix but the nuclei are well defined and there is less vacuolation of the cytoplasm. At the periphery the cartilage is diffusely pink stained. Here too the cells and nuclei are less well preserved. $\times 183$

C, ear necrocartilage implanted in the anterior abdominal wall for forty-four days. This tissue is better preserved. The nuclei are distinct. The cytoplasm shows moderate vacuolation. The matrix is irregularly mottled. Some portions show necrosis with only phantoms of the former structures. At the periphery there is a moderate amount of scar tissue. $\times 183$

D, specimen of ear necrocartilage refrigerated in merthiolate solution for forty-four days. Section shows an extremely well preserved piece of cartilage. The matrix is mottled, in portions being deeply pink stained while other portions are slightly blue stained. The cells are fairly well preserved though in some places moderately vacuolated. There are irregular areas of alteration where the cells are poorly preserved and the matrix diffusely pink stained. $\times 183$

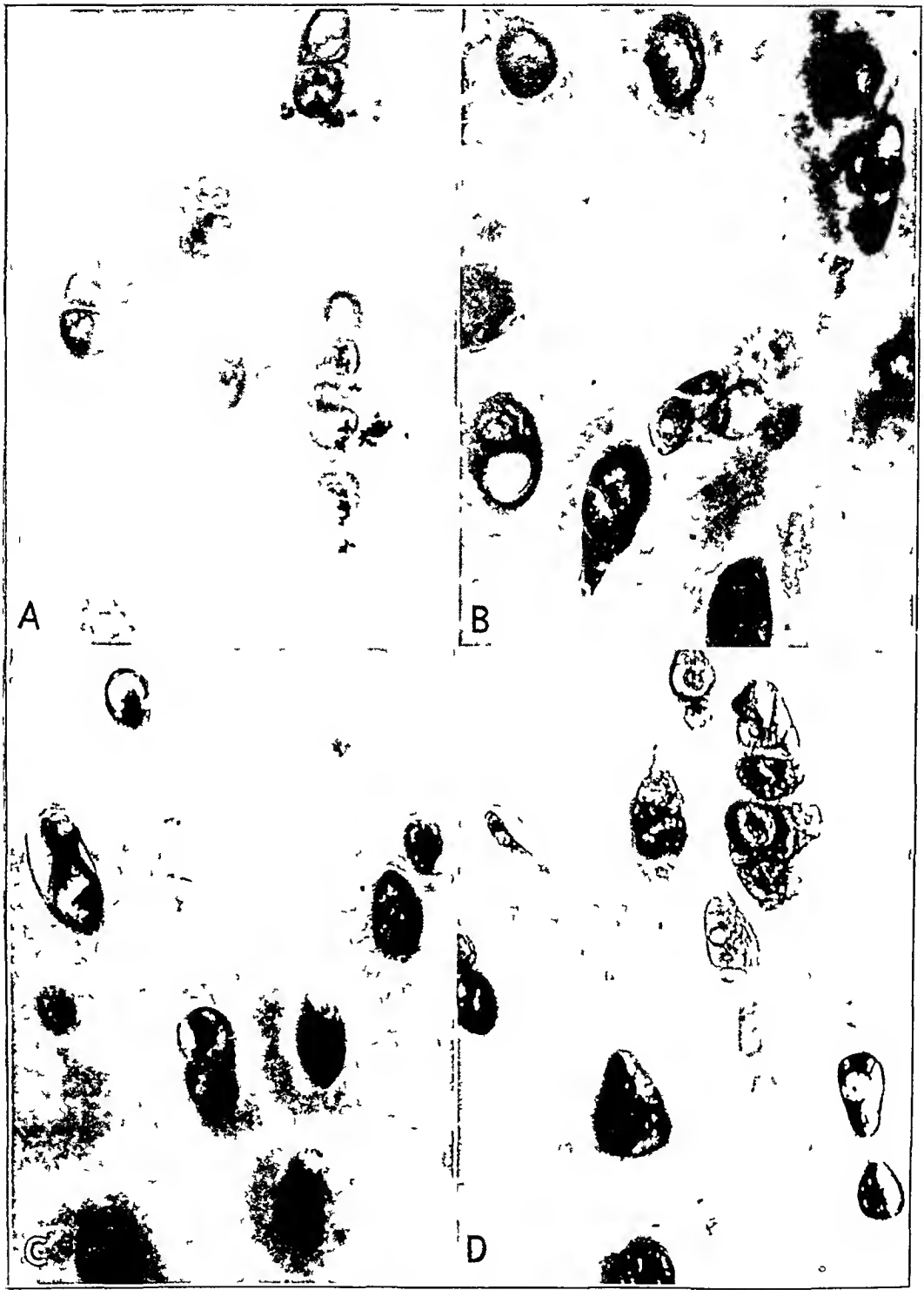


Figure 6

(See legend on opposite page)

easier to obtain and less apt to curl, patterns may be made more easily, and operation on the chest of the patient is not necessary. The disadvantages are: It is not as resistant to infection, and it may absorb without infection. He believes that experimental implantation of cartilage in animals or in the abdominal wall of patients is not exactly comparable to clinical use, because these beds are more amiable than those about the nose and face, where the cartilage is needed in reconstructive surgery. He further points out that preserving cartilage in alcohol causes a change in the cell nucleus which may erroneously lead to a diagnosis of necrosis.

HISTOLOGY AND PHYSIOLOGY OF CARTILAGE

Cartilage in the living apparently possesses no blood vessels of its own, often vessels separating adjacent tissues may pass through it³⁸. Besides its interstitial substances and cells, it contains a dense capsule and perichondrium. During fixation cartilage cells may easily become wrinkled, and this may be mistaken for pathologic change. Both the cells themselves and the interstitial substances differ appreciably in hyaline, elastic or fibrous cartilage.

The physiology is a moot point. Some workers have attempted to prove the existence of a system of canaliculi passing from one cell capsule to another through the interstitial substance of the cartilage. Organization of fibrils connecting adjacent cells has been discussed by some authors. Others believe these to be artefacts. In gross experiments nontoxic stains used on living cartilage demonstrate the dye to be quickly and easily absorbed by the interstitial substance. And so it is believed that cartilage *in situ* is permeated by tissue fluids from the perichondrium and in this way gains and maintains life.

When cartilage is excised regeneration does not take place, because the cells of mature cartilage do not divide in mammals. The defect is rapidly filled in with connective tissue, gained from the perichondrium or adjacent fascia. The fibroblasts of this granulation tissue produce capsules around themselves and often become transformed into new cartilage cells in the interstitial substance. The inter-

38 Maximow, A. A., and Bloom, W. A Textbook of Histology, Philadelphia, W. B. Saunders Company, 1938.

EXPLANATION OF FIGURE 6

A, specimen of rib necrocartilage placed in Bouin's solution for fixation. Section reveals a well preserved cartilage. The nuclei are well preserved for the most part. In a few places the cells are vacuolated. The matrix immediately around the cells is deeply blue stained but elsewhere it is pink. $\times 183$

B, rib necrocartilage implanted in the anterior abdominal wall for seven days. Two sections reveal fairly well preserved cartilage. At the periphery the tissue is diffusely pink stained and there is moderate dissolution of the cartilage cells. Toward the center the cells are large and deeply blue stained. In some places they are vacuolated. The nuclei are prominent. The matrix shows the usual light and dark blue coloration. $\times 183$

C, rib necrocartilage implanted in the anterior abdominal wall for forty-four days. Section shows well preserved cartilage cells. In some places the cells are moderately vacuolated but in other places they are well preserved. The nuclei are distinct. The matrix is diffusely blue stained toward the center and at the periphery pink stained. At the periphery there is dissolution of the nuclei and cells. $\times 183$

D, specimen of rib necrocartilage refrigerated in merthiolate-saline solution for forty-four days. The cartilage is fairly well preserved. At the periphery the tissue is diffusely pink stained. There is loss of cytologic detail here. Toward the center the cells are better preserved. The matrix presents the usual histologic appearance. $\times 183$

stitial substance of the scar tissue becomes homogenous and produces new interstitial substance, similar to that occurring in the embryonic development of cartilaginous tissue and thus cartilage is formed by metaplasia of the loose connective tissue

There are many aspects of the physiology of transplanted cartilage that we do not understand. When hyaline cartilage is taken from a rib or elastic cartilage from an ear and then transplanted in the same subject to some other site in the body, does it continue to live and obtain tissue fluid as we understand the life of normal cartilage, or is it a foreign body with a specific affinity to that individual because it is autogenous? Does live homogenous cartilage (transferred immediately from one subject to another) act differently physiologically than autogenous carti-

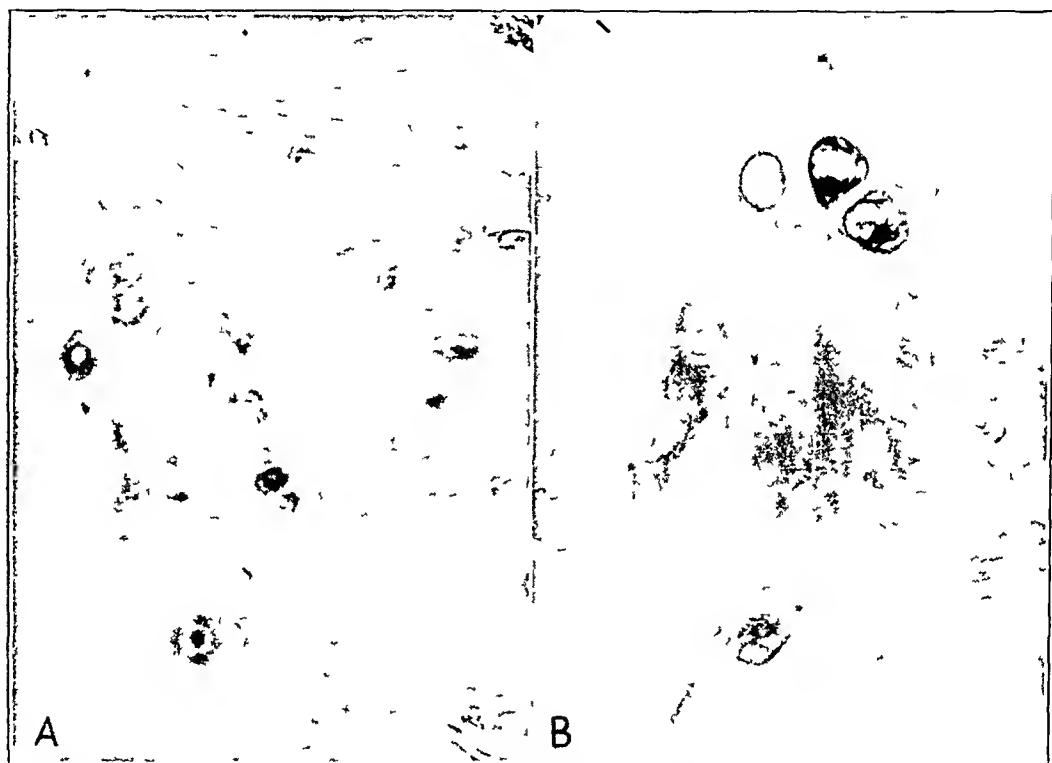


Fig 7—*A*, autogenous rib cartilage implanted in the anterior abdominal wall for two hundred and seventy days. Surrounding two pieces of cartilage can be seen abundant scar tissue. One piece of cartilage shows almost complete loss of the nuclear structure with diffuse pink coloring of the matrix. The other piece shows fairly well preserved cartilage toward the center with the usual nuclear and cellular structures. At the periphery there is dissolution of the architecture to some extent and dissolution of many of the cells. In the surrounding scar tissue can be seen a small piece of metaplastic bone. $\times 183$

B, autogenous rib cartilage implanted intranasally for two hundred and seventy days. Section shows an irregular piece of cartilage. Toward the center the cells are fairly well preserved. The matrix and cells present the usual appearance. At the periphery there is moderate dissolution of the cells and the matrix is diffusely pink stained. The cartilage is surrounded by considerable scar tissue. $\times 183$

lage? It has been the method for many years to hoard an excess of autogenous cartilage in a pocket of the abdominal wall. Does such cartilage continue to live in its new site or is it only a foreign body tolerated by the host?

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EVALUATION OF EXPERIMENTAL RESULTS

All of the microscopic sections and pathologic diagnoses were made by Dr Reuben Straus, pathologist to the Cedars of Lebanon Hospital. The photomicrography was carried on under his direction and supervision by Mr Donald Wald of the photographic department of the hospital.

In the first experiment (fig 2 *A* and *B*) ear necrocartilage was used (the donor had been dead for forty-eight hours and in refrigeration). The cartilage was preserved in solution of formaldehyde for four days, washed, then transferred to merthiolate-saline solution (1:4) for eighteen days. One piece was then placed in a pocket in the anterior abdominal wall of a patient, another continued on in the merthiolate-saline solution and refrigerated. After ninety-six days both

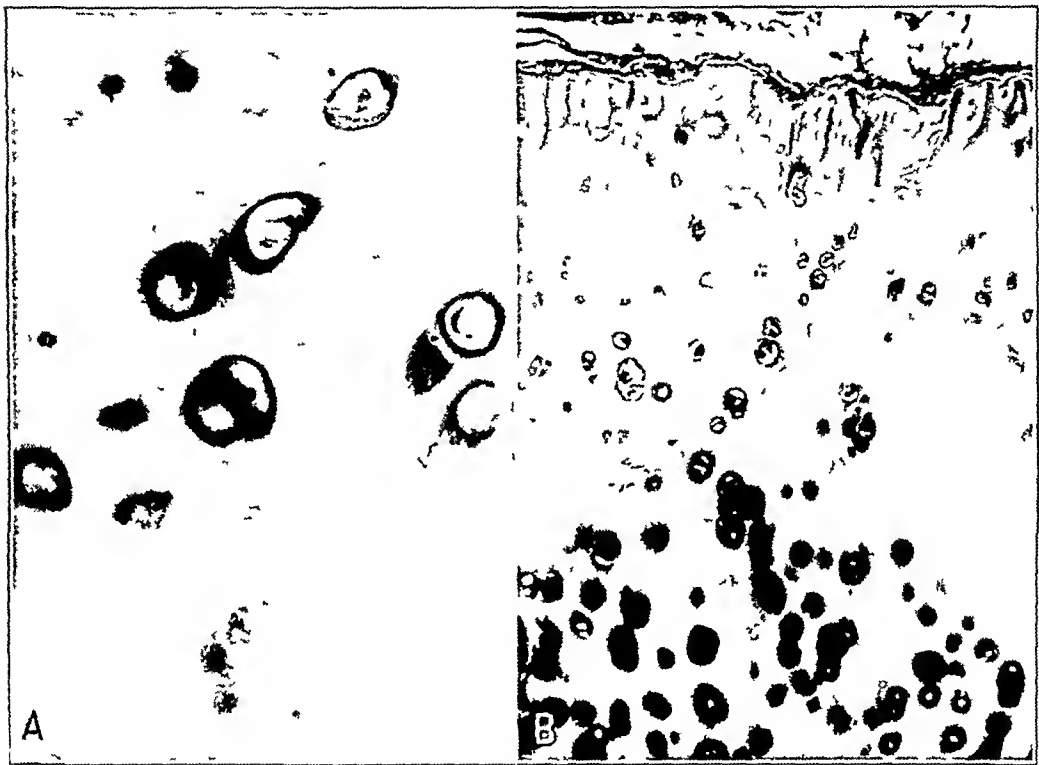


Fig 8—*A*, autogenous rib cartilage specimen implanted in the anterior abdominal wall for fourteen years. Section shows moderate fibrosis of the surrounding tissue. The cartilage presents a striking alteration from the normal. There are irregular areas of degeneration characterized by loss of nuclear and cellular structures and a diffuse pink cast to the matrix. There is an occasional small area of calcification, and in one area a small bit of bone metaplasia can be seen. In a few areas the tissue appears fairly well preserved and resembles fairly fresh cartilage. Here some of the cells are moderately vacuolated while in other places the cellular outlines and nuclear outlines can be seen. At the periphery of this section the cartilage is irregular. There is dissolution of the tissue and ingrowth of areolar tissue separating blood vessels. $\times 183$

B, autogenous rib cartilage, same as *A*. $\times 0.833$

pieces were gathered for pathologic study. That retained in the solution appeared better preserved microscopically. Grossly the cartilage taken from the abdominal wall had not decreased in size, even though much of it had been replaced by fibrous tissue. The ear necrocartilage from which these pieces were taken was used to

replace a partially absent ear. The former has now been implanted for fourteen months and clinically appears in excellent condition.

In the second experiment (fig 4 through 6 C) ear necrocartilage was compared with fresh ear cartilage and rib necrocartilage. A piece of cartilage was excised from the patient's opposite ear and employed as a control. A section of

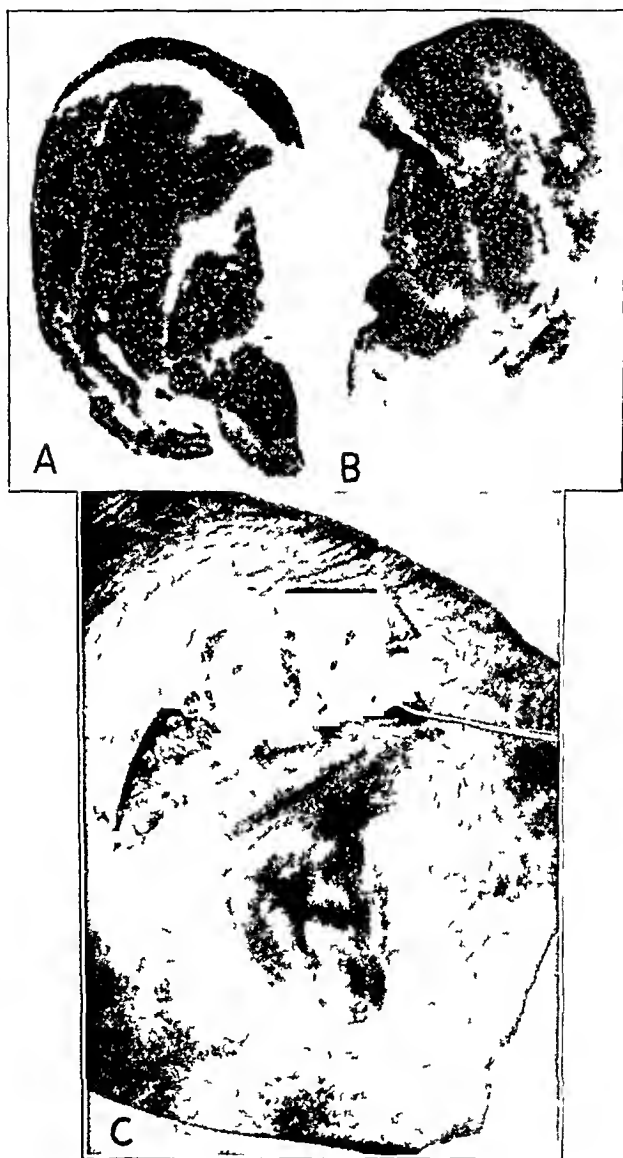


Fig 9—4, ear necrocartilage as seen from its anterior surface, indicating the intricate whorls and bizarre shape. Note especially on the outer inferior aspect that the cartilage spreads into a peninsula-like projection.

B, ear necrocartilage from its posterior surface with the perichondrium removed. The cartilage is placed in solution of formaldehyde and then refrigerated in merthiolate-saline solution until required. The body of the cartilage is then sieved with a dozen small holes so that the granulation tissue may rivet it into position when placed in the pocket.

C, ear necrocartilage being entered into its marsupial pouch at the operating table. The incision is approximated with silk and the skin gently teased into the interstices of the ear cartilage with the aid of alcohol-saturated cotton and small pieces of marine sponge.

each was placed in a pocket in the anterior abdominal wall of the patient and another kept in merthiolate-saline solution. Part was removed at the end of seven days, the remainder at the end of forty-four days and microscopic sections studied. The cartilage retained in the merthiolate-saline solution for comparison appeared in much better condition than that in the abdominal pockets. Grossly the cartilage removed from the abdominal pocket had not been reduced in size even though it had been invaded by fibrous elements. At the time this experiment

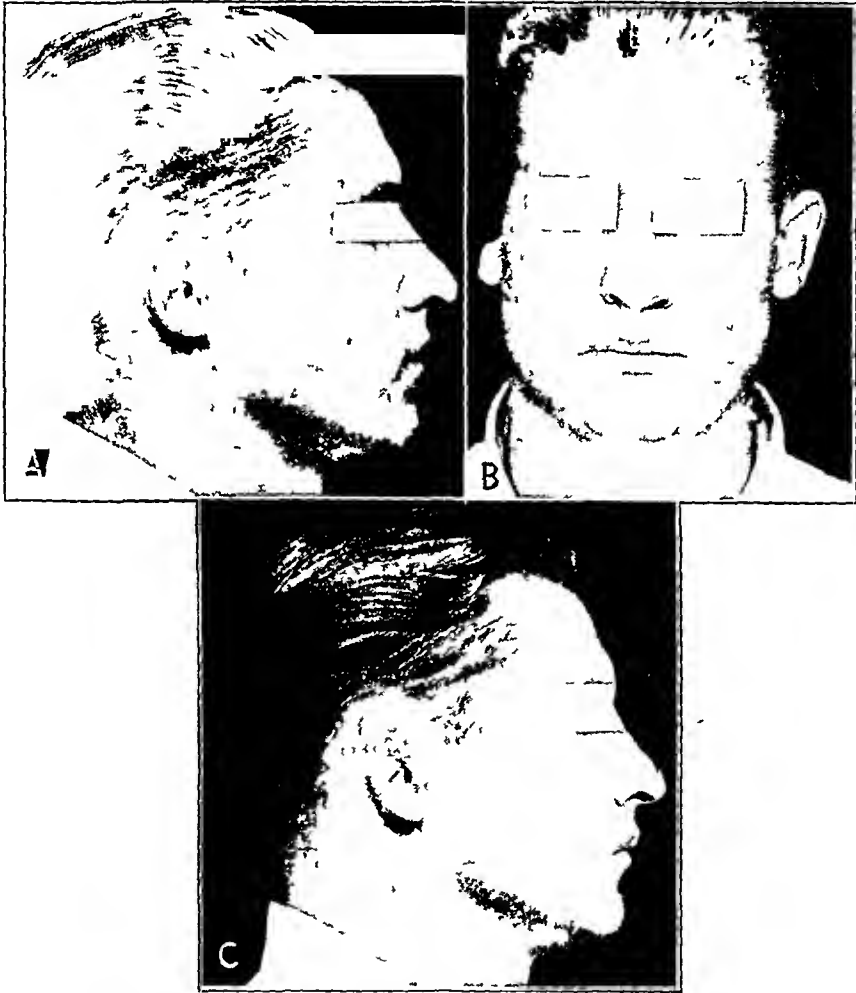


Fig 10—*A*, this patient had lost the whole upper portion of the ear, while retaining the lobule and a small amount of the concha. A plaster cast and photographs were made both of the good ear and of the affected one, so as to gauge the size and contour of the reconstructed member.

B, though it may be impossible to create an exact replica of the opposite ear, it is most important to construct one of a similar size and shape. Presurgical planning of all stages in the procedure is paramount.

C, two weeks after ear necrocartilage has been placed in a pocket created in the mastoid area. A clavicular tube pedicle is now being brought up to be grafted on the posterior surface of the reconstructed ear and to form the contour of the helix as required.

was begun the opposite ear of the dead person from which this necrocartilage was taken was implanted in the patient to reconstruct a totally absent ear. This ear

necrocartilage (fig 10) has at the time of writing been in place for one hundred and twenty-four days and clinically appears well preserved

In the third experiment autogenous rib cartilage was placed in the nose of a patient and a portion from the same rib was also inserted in a pocket in the anterior abdominal wall. At the end of two hundred and seventy days microscopic sections were made of each, and a study of both slides revealed little difference. It has been the contention of many that cartilage transplanted to the nose is in a totally different medium than that placed beneath the abdominal wall. Their logic was reasonable because of the presence of bacterial flora in the nose. However, our experiments (fig 7 *A* and *B*) indicate that transplanted cartilage does not act differently in either area.

It was our good fortune to gain a piece of autogenous rib cartilage that had been placed beneath the abdominal wall of a patient about fourteen years ago by the late Dr. Howard L. Updegraff (fig 8). Grossly the cartilage was well fixed by surrounding fibrous tissue, was firm and apparently had retained its identity. It is interesting that bone metaplasia had occurred in several areas, as it often does in normal cartilage in its own habitat.

RECONSTRUCTIVE SURGERY OF THE PARTIALLY ABSENT EAR

Partial absence of an ear, depending on the location of the missing part, suggests several methods of reconstruction. Should the defect be of the helix a small delayed flap borrowed from the mastoid tip, with its base at the margin of the defect may be folded on itself. The resultant raw surface on the mastoid area may then be covered with a thick split skin graft.

Reconstruction of the ear lobule may be carried out with a rectangular delayed flap from the neck, raised to the ear in one stage, then later severed from its base, leaving it sufficiently long so that it may be folded on the posterior aspect. The resulting defect on the neck may be undermined and sutured in a straight line. Dependent on the amount of tissue absent, a Gavello flap may be utilized for reconstruction of the lobule.

When the tragus is absent a delayed flap from the face, with its base posterior is turned on itself, and the resultant raw surface grafted. Other small defects of the auricle may be reconstructed by utilizing flaps from the mastoid area. Wherever framework is necessary, struts of preserved or necrocartilage may be used.

On occasion odd cases are reported in the literature concerning the resuturing of a totally or partially absent ear that has been severed and dropped to the ground. Obviously this is an impossibility. Also, ears or portions of ears cannot be taken from one person and transferred to another. However, in any case in which the ear or part of it has been severed from the head, the cartilage, after having been dissected from its tissues, may be kept in merthiolate-saline solution and refrigerated for future use.

Prosthesis—Various methods of making artificial ears have been devised. Bulbulian³⁹ has studied the problem extensively, using Latex. Of late, plastic materials have been utilized. Though the Latex is soft and pliable, its consistency is such that it does not offer a blending surface with the skin. On the other hand, plastic materials are soluble in alcohol with a blending surface tend to shrink and thus far have not been developed as a permanent prosthesis.

³⁹ Bulbulian, A. H. Prosthetic Reconstruction of Nose and Ear with Latex Compound, J. A. M. A. **116** 1504-1506 (April 5) 1941.

The prosthetic ear has a definite place as a temporary procedure. However, as a rule, the patient would rather have a surgically constructed one, even though it is not perfect, as long as it is made of tissue and the tissue is attached to his body.

SURGICAL METHOD OF RECONSTRUCTING THE TOTALLY ABSENT EAR

Preoperative Study—Careful photographic studies are made of the patient's head, which include the good ear and the affected one for comparison. Though it may be impossible to reproduce a replica of the good ear, the surgeon must attempt to obtain one of the same size and contour. Often it is necessary to place the unaffected ear closer to the head by removing the required ellipse of cartilage, so that it will not be too prominent in contrast with the reconstructed ear.

A plaster cast is made of both ears, they are studied and compared. The model of the affected ear is then built up with clay, so as to gauge the ear necrocartilage required.

Surgical Procedure—**First Stage** A curved incision about $1\frac{1}{2}$ inches (3.8 cm) long is made on the posterior aspect of the mastoid area. The blade is carried through to just above the superficial fascia. Through the elliptic incision the skin is carefully undermined and a pocket created that will house the future ear cartilage. The flap is made as thin as possible and yet thick enough to carry circulation for its latent chore. Thinness is desired so that the flap may drape itself well into the convolutions peculiar to the ear cartilage, in this case ear necrocartilage. Bleeding is controlled, the flap is allowed to return to its bed, and the incision sutured.

In two or three weeks the flap is again raised. This may be repeated a third time if necessary, in order to obtain as thin a flap as possible, so that the skin may envelop itself into the interstices of the whorls of the ear necrocartilage.

Second Stage The ear necrocartilage has been previously prepared by meticulously removing the tissue and perichondrium. A dozen small holes have been made in the body of the cartilage, to allow the granulation tissue to rivet through and hold it in place when implanted.

The thin delayed flap over the mastoid area is raised again, bleeding carefully controlled and the ear necrocartilage placed in its previously prepared marsupial pocket. Cotton saturated with alcohol and small pieces of marine sponge are used to tuck the skin into the convolutions of cartilage. Sulfanilamide crystals are thinly spread into the pocket, both to avoid infection and possibly to help create fibrosis.

A clavicular tube pedicle is started at this time. Its dimensions are such that it may be waltzed up the neck to the ear area. It is made some $4\frac{1}{2}$ inches (11.43 cm) long and $1\frac{1}{4}$ inches (3.18 cm) wide. We avoid neck tubes when possible so that no disfiguring scars remain. The tube pedicle is severed from its anterior connection in three or four weeks and waltzed to a trap door on the neck. In another three or four weeks it is brought to the base of the ear, in another month to a position of a new helix. The time required in these cases may be shortened by moving the tube pedicle more quickly, as pointed out by Douglas and Buchholz.⁴⁰

Third Stage An incision is now made one-fourth inch (0.64 cm) above the necrocartilage at its periphery and carried from the anterior-superior aspect of the ear some 3 inches (7.62 cm) around posteriorly down to the fascia.

The tube pedicle is opened and allowed to inhabit itself within the incision. Laterally, slightly away from the head, the tube is fashioned to simulate a helix, while behind the ear necrocartilage now serves as a thick covering.

We discarded the use of an Esser outlay to reconstruct the posterior aspect of the ear, as it is often disfiguring and frequently allows the ear to collapse. We have not found it necessary to cast the ear so far away from the head but prefer to bring the opposite ear closer, making the two conform.

SUMMARY

When necrocartilage, homogenous or autogenous cartilage is implanted in the human being, it is probably a foreign body, but the host makes no effort to expel it. Necrocartilage has been refrigerated in merthiolate-saline solution for several

⁴⁰ Douglas, B., and Buchholz, R. R. The Blood Circulation in Pedicle Flaps. *Ann Surg* 117:692-709 (May) 1943.

months and then implanted in various parts of the body. Healing has been rapid, with virtually no local reaction.

Our experiments reveal that not only is necrocartilage invaded by fibrous tissue, but often, too, autogenous cartilage. In the cases in which the specimens of necrocartilage in the abdominal wall were invaded by fibrous tissue, cartilage from the same specimen used for ear framework maintained its strength and identity, so that even though one may conclude that it, too, had been invaded with fibrous tissue, clinically it was serving its purpose.

Concurrently we have been carrying on similar experiments with rib necrocartilage and implanting the specimens in bodily structures other than ears, i. e., the nose, the forehead, the jaw, the eye socket, etc., and we shall report these studies when the experimental work is completed.

My assistant, M. Suzanne Postelle, R.N. (Mayo Clinic), helped to gain the cooperation of the patients, making this work possible, and my secretary, Mary King, R.N. (Univ. of Indiana), assisted me by doing editorial proof reading.

REVIEW OF UROLOGIC SURGERY

ALBERT J SCHOLL, M D
LOS ANGELES

FRANK HINMAN, M D
SAN FRANCISCO

ALEXANDER VON LICHTENBERG, M D
MEXICO CITY, MEXICO

ALEXANDER B HEPLER, M D
SEATTLE

ROBERT GUTIERREZ, M D
NEW YORK

LIEUTENANT COMMANDER GERSHOM J THOMPSON (MC), USNR

EDWARD N COOK, M D
ROCHESTER, MINN

EGON WILDBOLZ, M D
BERNE, SWITZERLAND

AND
VINCENT J O'CONOR, M D
CHICAGO

KIDNEY

Anomaly—Hanley¹ reports a case of horseshoe kidney and a supernumerary kidney and a case of a triple kidney with a horseshoe component

He states that a supernumerary kidney is a distinct rarity in itself. Of the numerous cases reported as examples of this condition, many are merely instances of double or fused kidneys, while others are insufficiently described for accurate classification. Only 43 authentic cases of supernumerary kidney are found in the literature. In the majority of the reported cases the extra kidney was below the normal one, usually on the left side, and more often than not rudimentary. The ureter may join its fellow or end extravasically, while the termination in many cases is unstated. A normal separate ureter is apparently rare.

In Hanley's case the supernumerary kidney was above its fellow and was not rudimentary, and its ureter was complete throughout its length, opening into the bladder by a separate orifice. The chief interest, however, lies in its association with a horseshoe kidney—a combination previously unrecorded.

In the first case the patient was a man aged 30 years who had repeated attacks of pain in his right loin. Cystoscopy and roentgenologic examination showed that the lower group of calices of the right kidney were medial to the ureteral line, indicating a horseshoe kidney. On the left side, the lower pole of the horseshoe kidney was small. Above this, reached through a second ureter, was a comparatively normal-sized kidney. At operation, the right kidney was found to be slightly enlarged, the lower pole sloping across and forming the isthmus of the kidney. The left side was palpated, and it was found that the left half of the horseshoe kidney was smaller than the right and somewhat lower. Above this was a mass which was construed to be the third kidney. This was lying in contact

* The opinions and assertions contained herein are the private ones of the various writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

¹ Hanley, H G. A Horseshoe and a Supernumerary Kidney. A Triple Kidney with a Horseshoe Component, *Brit J Surg* 30 165-168 (Oct) 1942.

with the horseshoe kidney but was freely movable and not connected to the left half of the horseshoe kidney

The second case was that of a male child aged 3 days, who died. At necropsy the child was found to have a complete transposition of viscera. A horseshoe kidney was found with three pelves and three complete ureters opening into the bladder separately.

Goldstein and Abeshouse² present 8 cases of horseshoe kidney. Six of the patients had definite renal disease and symptoms of some nature, and 2 were without renal disease or symptoms. Heminephrectomy was performed on 2 of the 4 patients who were operated on. All the operations were extraperitoneal. In the 4 cases observed at operation thick parenchymal tissue formed the isthmus at the lower poles, and the renal artery came from the abdominal aorta. No immediate or late deaths resulted from the surgical treatment. If horseshoe kidneys are exposed because of renal disease, hemisection should be performed after the pathologic process has been corrected. Horseshoe kidneys that have small calculi in the calices should be heminephrectomized. Horseshoe kidneys causing pain or other symptoms without renal disease should be sectioned.

Anomalous Vessels—Shupe³ states that in numerous cases aberrant renal vessels have been divided for hydronephrosis with good results and with no necessity for any further operation. In occasional cases, however, there will be an infarct of such a size that nephrectomy will become necessary. Shupe reports a case in which a large aberrant renal vessel the size of a slate pencil was divided without causing a renal infarct.

The patient was a girl aged 16 years who had a mass in the upper left quadrant of the abdomen. Cystoscopic examination and bilateral pyelograms revealed a large hydronephrosis of the left side with obstruction at the ureteropelvic junction. At operation, an artery the size of a slate pencil was found coming from the aorta and entering the lower pole of the kidney. The aberrant vessel was in direct contact with the ureter close to the ureteropelvic junction and acted as a sling over which part of the extrarenal pelvis was dependent. At operation the aberrant vessel was divided and ligated, and the scar tissue surrounding the ureteropelvic junction was freed by sharp dissection. The ureter then straightened out, and the pelvis began to empty. A blanching of the posterior surface of the lower pole of the kidney was noted. This blanching took in a third of the surface of the kidney. Neither the pelvis nor the kidney was incised.

The patient was free from pain and tumor for fourteen days, at which time the pain and swelling reappeared, together with an elevation of temperature. Nephrectomy on the left was advised and performed. At the operation there was no sign of any difference in color or structure of the lower or upper pole. One part of the kidney seemed just as vascular as another. A large hydronephrosis was present, and the ureter and renal pelvis were bound down by a mass of adhesions. These were carefully dissected free from the pedicle, and the kidney was removed.

The patient had an uneventful convalescence following nephrectomy and left the hospital on the thirteenth day.

Young⁴ discusses Shupe's paper on the division of aberrant blood vessels to the kidney. The demonstration that they can be divided without the production of

2 Goldstein, A. E., and Abeshouse, B. S. Surgical Treatment of Diseases of Horseshoe Kidneys, *J. Urol.* **49** 42-54 (Jan.) 1943.

3 Shupe, T. Division of Aberrant Blood Vessel to the Kidney Without the Production of an Infarct, *Tr. Am. A. Genito-Urin. Surgeons* **35** 15-19, 1942.

4 Young, H. H., in discussion on papers of Jeck and Orkin,⁶¹ Shupe,³ Howze and McKenna, Kiefer and Bronstein, *Tr. Am. A. Genito-Urin. Surgeons* **35** 59-60, 1942.

infarct is important. Young employs an anterior abdominal incision in these cases. The incision begins at the outer side of the rectus muscle, about 1 inch (2.5 cm) above the pubes, and is directed obliquely upward and outward to the cartilage of the tenth rib. The incision, in fact, passes over the cartilage so as to make a longer cutaneous incision and allow wider retraction. The fasciae and muscles are divided, and then the peritoneum is stripped back until the ureter is exposed at a point several inches below the kidney. Following the ureter upward and continuing the separation of the peritoneum, the ureteropelvic juncture is exposed as it lies in its natural position and then the pelvis above it. This affords an excellent opportunity to study the pathologic changes *in situ* before they have been disturbed by freeing the kidney and drawing it far out, as must occur when the usual lateral oblique renal incision is employed.

In 1 patient of whom Young showed motion pictures, a thick vascular cord was found passing across the ureteropelvic juncture to the lower pole of the kidney. Associated with it were pronounced adhesions, which were divided. Above the vascular cord, the ureter was much kinked, and it entered the pelvis beneath the vascular cord. Although the adhesions were freed, the considerably dilated pelvis did not empty itself until the vascular cord had been elevated, triply clamped and divided. Immediately after this, the ureter straightened out and peristalsis began.

The motion picture beautifully demonstrated successive peristaltic waves which started in the pelvis as it gradually emptied and passed down the ureteropelvic junction and along the ureter. These were so active that the ureter actually was seen to move and twist, almost like an earthworm. Investigation showed that no stricture of the ureter was present, only a thinning of the wall at the point where it was compressed by the vascular cord. After division of the cord, a small area of the lower pole of the kidney turned bluish black. The rest of the kidney appeared normal.

In cases such as this, it is not necessary to isolate the lateral, upper and posterior surfaces of the kidney at all. At the ureteropelvic juncture any pathologic conditions which may be discovered can be attacked, often at once, without disturbing the kidney in its bed or isolating the vessels of the pedicle. In cases in which the obstruction is due to aberrant vessels, one almost always finds that they pass in front of the ureter. This is another argument for the anterior incision which is also applicable in cases of kinks or strictures and is particularly appropriate when the Y-V plastic operation is carried out. If it is desirable to perform nephropexy, no difficulty is experienced in isolating the kidney and carrying out an appropriate technic through this same incision. When it is desirable to expose the ureter well down toward its lower end, the anterior incision has much to recommend it, inasmuch as one can easily follow the ureter down to its juncture with the bladder and perform complete nephroureterectomy through one incision. The anterior incision is also of great advantage when in dealing with wounds and other types of traumatism it is desirable to explore the peritoneal cavity and perhaps operate on other viscera, as is often the case in war surgery.

When this technic is employed, Young provides drainage through a stab wound over the crest of the ilium. This gives direct retroperitoneal external dependent drainage, which is always desirable for a few days. If one wishes to drain the lower end of the ureter, another Penrose drain or tube may be brought out through the lower angle of the oblique abdominal incision.

Tumor—Grauhan and Hellriegel⁵ state that the infiltration of renal tumors through the anatomic capsule is fairly common but that a complete bursting of

5 Grauhan and Hellriegel. *Berstende Nierentumoren*, *Ztschr f Urol* **35** 409-417, 1941

the growth is rare. This extraordinary complication has, clinically and anatomically, an acute explosive character and causes complete destruction of the tumor.

They report 2 cases of this type. At the onset there are signs of acute abdominal disease with heavy pains in the renal region and in the hypogastrium. In some cases conditions suggest extensive abdominal hemorrhage, and it may be impossible to make the diagnosis except by laparotomy. Early nephrectomy is the only satisfactory treatment. At the operation there is usually extensive hemorrhage in the perirenal tissue, starting from a wide crater in the malignant region in the kidney. Pieces of tumor tissue of various sizes are usually found scattered in all directions by the vigorous blood stream. In both reported cases the tumor was an angioliposarcoma, a combined neoplasm of connective tissue character. Epithelial constituents were usually not found. Unlike malignant sarcomas of the kidney, these angioliposarcomas are rather benign. In some reported cases, no recurrence had been found seven years after operation. The authors suggest a relation of this condition with tuberous sclerosis of the cerebrum, a disease in which a similar type of combined renal tumor is found in a large percentage of cases.

Hale and Burkland⁶ state that renal tumors usually produce symptoms which may be misinterpreted because they are not directly referable to the genitourinary system. Urinary findings may be scant or completely absent. A normal urine does not rule out the presence of renal tumor. The classic triad—palpable tumor, hematuria and pain—is a late manifestation and is of no value in the early diagnosis of renal malignant lesions. Distant and multiple metastatic growths are frequent. These may give rise to symptoms before the primary growth. Hematuria is the most important and frequent symptom of renal tumor. Among elderly male patients the presence of gross hematuria involves a differential diagnosis between renal neoplasm and benign prostatic hypertrophy. In the diagnosis of renal neoplasm, one must consider all the facts contributing to the diagnosis and not place too much reliance on such isolated findings as are revealed by pyelography.

Bugbee⁷ discusses adenoma of the kidney with associated lesions, reporting 3 cases. He states that adenoma of the kidney is usually small and may be single or multiple, it may be grayish or yellow and appears in the cortex just beneath the capsule, as in the first 2 cases here reported. Large adenomas are exceedingly rare. Adenomas of the kidney are essentially benign, but the dividing line between normal epithelium and adenoma, or between adenoma and carcinoma, may often be difficult to define. The small, often multiple, adenomas are sharply demarcated and consist of a mass of small tubules packed closely together, showing no glomeruli. A part or all of the cells may be arranged in groups which have no lumens, or the ducts may be dilated and show epithelial hyperplasia or papillary projections. In another type designated as alveolar, the pattern may simulate adrenal rests, a fact which has given rise to much discussion as to its pathogenesis. In this type the cells are cuboidal or cylindric. They may be granular and free of fat, or they may contain a large amount of fat.

The first case was of a man aged 43 years who gave a history of pain in the left flank twenty years before. Nephrectomy was done on the left side. The kidney was three times normal size, there was a sharp kink in the ureter at the uretero-pelvic junction, and a large anomalous vessel passed to the upper pole. Pathologic examination revealed hydronephrosis and adenoma of the kidney.

6 Hale, N. G., and Burkland, C. E. Unrecognized Renal Tumors. A Study of Fifty-Four Cases in 6,577 Autopsies, and Personal Cases, *J. Urol.* **49**: 426-431 (March) 1943.

7 Bugbee, H. G. Adenoma of the Kidney with Associated Lesions. Report of Three Cases, *Tr. Am. A. Genito-Urin. Surgeons* **35**: 97-108, 1942.

The second case was a woman aged 57 years who complained of intermittent attacks of hematuria of several hours' duration, which were so severe that she was left exhausted. Cystoscopic and roentgenologic examinations showed the right kidney to have deficient function; the urine from this kidney contained blood and pus cells and roentgenograms showed the presence of two renal calculi, the findings for the left kidney were normal. The right kidney was removed and found to be largely destroyed and pyonephrotic. In the upper part of the wall of the pyonephrotic sac there was a yellowish tumor 3.5 cm in diameter and 2.5 cm in thickness. The histologic structure was that of an adenoma.

In the third case, a man aged 54 years complained of a constant aching pain in the right costovertebral angle which had been present for three weeks and of occasional backache for several years. Cystoscopic investigation revealed a functionless right kidney and a normal left kidney. The right kidney was removed and found to be twice normal size. It contained a mass about 4 cm in diameter. The diagnosis was papillary adenoma of the right kidney with tuberculous abscess of the lower pole.

Bugbee concludes that it seems probable that adenomas of the kidney occur most frequently late in life, in kidneys which are the seat of vascular disease, a circumstance which suggests that adenomas are the result of proliferative reaction on the part of the tubules which have been cut off from the primary blood supply as in hydronephrotic sac, pyonephrosis or infection, such as tuberculosis. Small adenomas will seldom give rise to symptoms but should be borne in mind as a possibility when one is dealing with any case of hydronephrosis or renal cyst.

Cysts—Fister⁸ gives four convenient classifications of renal cysts: simple, solitary, serous, hemorrhagic, small multiple and multiple, including multilocular. Simple serous cysts may be congenital or acquired, and the mechanism of production is probably the same. They may be present at any age and are perhaps more frequent in the male than in the female sex. The origin is most commonly parenchymal, the location is usually unilateral, and the lower pole is more frequently involved than the upper. Localizing symptoms may be absent, or there may be severe renal colic. Diagnosis is chiefly dependent on roentgen findings, although it is not always possible to make a preoperative differential diagnosis. Good pyelography and intravenous urograms are the best diagnostic aids. In the absence of associated renal disease and if the cyst is not too large, excision is the method of choice. Nephrectomy is indicated when concomitant renal lesions exist.

Rathbun⁹ discusses polycystic disease of the kidneys. A study of a group of cases of this condition has led him to believe that the prognosis as to longevity is perhaps a bit better than is commonly supposed, that a fair proportion of the patients present symptoms of interest to the urologist and that a few may be subjected to operation with a reasonable expectation of improvement and prolongation of life. He believes that there are two fairly distinct types of this disease. One is noted in newborn infants, while the other, the type most commonly discussed, develops in middle or late adult life. Occasionally it is reported as present in the newborn and more frequently as occurring in persons in the fifth and sixth decades, but it is practically never noted in persons in their teens and seldom in young adults. While of course it is quite possible that these two types may represent different degrees of the same condition, the gross appearances and the histologic pictures plus

8 Fister, G. M. Simple Serous Cysts of the Kidney, *J. Urol.* **49**: 408-414 (March) 1943.

9 Rathbun, N. P. Random Thoughts on Polycystic Disease of the Kidneys, *Trans. Am. Genito-Urin. Surgeons* **35**: 131-145, 1942.

the age incidence suggest that they may well have different embryologic backgrounds

Rathbun's paper is based on a study of 16 cases observed over a period of fifteen years, plus 1 case observed previously and included because of its particular interest. Of these 17 cases, 8 were recognized clinically but did not come to necropsy, 9 were found at necropsy, and in some of these the diagnosis had been assumed but had not been definitely determined. The age incidence of the entire series was as follows. Seven patients were infants, either stillborn or in the neonatal period. The youngest adult was aged 20 years. Another patient was aged 38 years. The remaining 8 were in their fourth, fifth and sixth decades, the oldest being aged 69 years. The average age of the adults was 51.7 years.

In 5 of the 9 cases in which necropsy was performed, other congenital anomalies were noted. They included congenital cystic liver, absence of the left kidney and the left testicle and congenital deformity of the anal orifice. In 14 of the cases polycystic kidneys were proved to be bilateral. In 1 case of unilateral polycystic kidney there was absence of the remaining kidney, while in another the presence of polycystic disease in the contralateral kidney was suspected but not proved. In still another case polycystic kidney was noted in one half of a horseshoe kidney, the other half being perfectly normal. Two pairs of sisters were noted among the infants, 1 pair occurring in consecutive pregnancies.

With one exception the pathologic picture in the postmortem specimens for the newborn infants was typical. The kidney or kidneys were enormously enlarged almost filling the abdomen. On microscopic examination the kidneys were found to consist almost entirely of interstitial fibrous tissue with only an occasional tubule and glomerulus, and all of those were grossly deformed.

Of the 10 adults studied clinically, 4 were constantly hypertensive, 3 were intermittently hypertensive and 1 had normal blood pressure. Two were definitely hypotensive. It is generally understood that hypertension is part of this disease. Of the 8 patients in the adult group whose disease was recognized clinically, 5 were subjected to Rovsing operations. In 3 of the 8 clinical cases there were no urologic operations. One adult was alive and in fair health seven years after the diagnosis of bilateral polycystic disease was made. Another adult lived for one year and died from renal insufficiency. In a third adult the polycystic kidneys were recognized during an exploratory laparotomy. At the time no operative treatment was carried out because the patient's condition was considered critical. The patient died three months after laparotomy.

Herman,¹⁰ in discussing Rathbun's paper on polycystic disease of the kidney, states that during the last year he has had 3 cases in which the condition was not recognized until operation, which rather changed his opinion that diagnosing polycystic disease was a fairly simple matter. Two of the patients were Negroes, one an old woman and the other a man aged about 35. Both of them had large tender masses on one side, pyelograms of the other side showed a normal condition. Herman thought the cases were clearcut instances of pyonephrosis, but exploration showed polycystic kidney. The disease is bilateral undoubtedly, but in these cases on the apparently uninvolved side the defect had not progressed to a point at which it was demonstrable. The third patient was a woman aged 65 years who had come for examination two years before the time of the report, suffering from hematuria. Herman discovered that she had a large congenital single kidney. There was no ureter on the opposite side, and the trigone here was undeveloped.

¹⁰ Herman, L. in discussion on papers of Hoch, Rathbun,⁹ Smith and Strasberg,³⁰ Hamer and Mertz,⁴⁴ and Ormond, Wadsworth and Morley, *Tr. Am. A. Genito-Urin. Surgeons* **35**: 183-184, 1942.

A secretory urogram was made which showed a defect suggesting a neoplasm. The patient went home, and Herman had forgotten all about her when more than two years later her physician called up and said she had had a sudden severe pain in the right loin three days before, which was followed by hematuria and anuria. She was semicomatose when brought to the hospital. Her ureter was catheterized, some heavily concentrated retained urine was drained off, and her renal function was slowly restored. After about two weeks of catheter drainage, her concentration of urea came down from 70 mg per hundred cubic centimeters of blood to normal, then Herman did a retrograde pyelogram. Her kidney was displaced outward and was rotated so that the medial border was pointing forward partially. The stereoscopic study showed the ureter projected forward, and the deformity did not suggest polycystic disease. It had the usual features of back pressure.

Surgical exploration then was performed. A cyst about as big as a walnut was found on the convex border slightly anteriorly, together with four or five smaller cysts, and at the lower pole of the kidney there was a cyst about the size of a large orange. A sudden hemorrhage had occurred into this, pushing the ureter forward and kinking it, this was the obvious cause of her difficulty. Herman opened the cyst and, fearing he might precipitate a hemorrhage, removed only part of the blood clot and put a drain in. The patient had an uneventful recovery. She was entirely well at the time of discussion.

Rupture—Ferrier and Knigge¹¹ review 137 cases of ruptured kidney. There were 37 deaths, or a mortality rate of 27 per cent. Six of these occurred in patients who had received stab or gunshot wounds through the kidney, although the cause of death was peritonitis due to associated intra-abdominal injury. The other 31 deaths were in the group of patients who had suffered associated multiple visceral or skeletal injuries, of which the renal trauma was only a minor part. The pathologist gave importance to renal hemorrhage in only 5 of these cases. If one considers merely these 5 cases in which renal hemorrhage was mentioned by the pathologist as a cause of death and excludes the rest of the 31, it leaves 5 deaths in a total of 111 cases, a mortality rate of 4.5 per cent. Even in these 5 there were other grave injuries at least as important as the renal injury.

There were 24 cases of moderate trauma, in these all the patients recovered without surgical intervention.

In 69 cases of extensive rupture of the kidney, many with extravasation, all the patients recovered. Twelve received surgical treatment.

There were 13 cases of stab and gunshot wounds of the kidney with 6 deaths due to intra-abdominal involvement. No attempt at repair of the kidney had been made in the cases in which recovery occurred.

Of 31 cases of severe general injuries, injury of the kidney was named as the cause of death in only 5. Because of associated grave injuries, it is doubtful if surgical treatment directed to the kidney would have done other than hasten death.

Foreign Body—Boeninghaus¹² reports the case of a man who had a foreign body in the renal pelvis. Ten years before, the patient swallowed some pieces of metal. A few of them were eliminated by the intestinal tract, and a few were removed by laparotomy. Three years later he had a perinephric abscess on the right side, and six years after this there was chronic purulent unilateral pyelonephritis on that side. Roentgen examination showed a large triangular stone in the right pelvis in which were embedded two metallic foreign bodies. Nephrectomy

11 Ferrier, P. A., and Knigge, W. Ruptured Kidney, *J Urol* **49** 457-459 (March) 1943

12 Boeninghaus, H. Fremdkörper im Nierenbecken, *Ztschr f Urol* **36** 86-89, 1942

was carried out but was extremely difficult because of extensive adhesions. The pathologicoanatomic examination revealed that the metallic body had passed through the wall of the duodenum into the peritoneal region and had caused the perinephric abscess. The metallic body then passed into the right kidney at its upper pole, migrating to the pelvis, after which the renal stone was built around the body which formed the nucleus.

Stone—Egger¹³ discusses the problem of recurrence of stone. He states that it is difficult to influence the different chemicophysical factors of the urine, such as colloidal production and surface tension. The danger of recurrence is four times greater in cases of operative removal of the stone than in cases in which it has been eliminated by conservative measures through the natural passages. Egger believes that the deciding biologic factors of recurrence occur in the first few days after operation. This is due to diminished output of urine caused by diminished arterial circulation, which in turn is the result of frequent subcapsular hemorrhages and postoperative edema of the parenchyma. Diminution of the urinary output gives a high specific gravity of the urine which disposes to fresh crystallization of renal concretions. Egger suggests decapsulation and denervation to counteract these factors.

Egger reports 3 cases of operative removal of renal stones in which decapsulation and denervation of the involved kidney had been carried out. This was done on the basis that by decapsulation the compression of the arterial blood supply is reduced. By denervation, the vasoconstrictor factors are eliminated. This causes an increased arterial flow to the kidney and an increased production of urine with a low specific gravity, also a favorable influence on the opposite kidney by elimination of certain renorenal reflexes is probable.

Nephrotomy—Barelare and Vest¹⁴ describe a new method of closure after nephrotomy which eliminates postoperative hemorrhage and reduces strangulation of cortical tissue to a minimum. The nephrotomy opening is closed with a form of mattress suture, the free ends of which are brought to the outside through the skin of the flank, where they are put under moderate tension by attachment to rubber bands. The tension is released shortly after operation by detaching the rubber bands. Thus the renal tissue is not strangulated by permanent ligatures. In case of primary or secondary hemorrhage, bleeding from the cortex can be easily controlled by reapplying the tension. The results of the use of this method in the repair of nephrotomy wounds were studied in the dog. Kidneys sutured in this manner did not suffer as much cortical damage as those sutured with conventional permanent sutures, as evidenced by study of corrosion models of the renal circulation.

Counterbalance—Hinman¹⁵ defines the condition of renal counterbalance. Experiments with renal resection demonstrate that compensatory hypertrophy is the result of stimulation and that equivalent portions of separate renal masses respond similarly irrespective of any disproportion of size. Glomeruli and tubules of the small renal remnant become hypertrophied to the same degree as those of the larger renal mass. The functional contribution of each will increase in proportion to this compensatory growth.

13 Egger, K. Decapsulation und Entnervung als Ergänzung zu den organerhaltenden Eingriffen bei Nierenstein und ihre Bedeutung für die Prophylaxe des Rückfalls, *Ztschr. f. urol. Chir. u. Gynäk.* **46** 184-198, 1942.

14 Barelare, B., Jr. and Vest, S. A. The Use of Elastic Tension Sutures in Nephrotomy Wounds, *J. Urol.* **49** 60-68 (Jan.) 1943.

15 Hinman, F. The Condition of Renal Counterbalance and the Theory of Renal Atrophy or Disuse, *J. Urol.* **49** 392-400 (March) 1943.

Experiments with the repair of hydronephrotic kidneys demonstrates that renal tissue injured by urinary back pressure has a remarkable capacity for repair, that this potency is enhanced by stimulation or the need of repair through renal insufficiency and is shown at its utmost when the demand is gradually increased, that inhibition of activity by such complicating factors as infection and imperfect relief of obstruction will affect the degree of repair and of hypertrophy as well as their permanence, and that a repaired hydronephrotic kidney disabled in any way by degenerative changes will atrophy progressively, and total function eventually will be taken over by the healthy, more capable compensatory mate

A true condition is defined by the conception of renal counterbalance as the bilateral adjustment to a permanent status of carrying total function after the removal of injury or disease. The probable renal changes (of repair, of hypertrophy and of atrophy) and the simple principles (related to the potentials of functional stimulation and renal reserve power) by which these changes consummate a counterbalance should be considered fully in every clinical problem of renal repair and restoration of function

PYELOURETERAL CHANGES IN PREGNANCY

Van Wagenen and Jenkins¹⁶ state that some dilatation of the ureters and renal pelvis usually exists in the latter half of pregnancy in the rhesus monkey. The first evidence of change of the tonicity of the urinary tract is stasis. A slower rate of excretion of the intravenously injected agent and the possibility of visualizing a longer column of fluid indicate the appearance of atony as early as the second month. Dilatation of the upper part of the urinary tract can develop after the removal of the fetus if the placenta remains functional. When established at the time the fetus alone is removed, the dilatation will persist and even increase before spontaneous expulsion of the placenta at term. The distention of the ureter and renal pelvis occurs more often and is more marked on the right side than on the left, as in man, and may be bilateral. Lengthening of the ureters is also present in the monkey, but to a less degree. Although there may be a residual increase of size of the ureter after one pregnancy, there appears to be no definite progressive injury to the ureter as a result of repeated gestation per se. The greatest dilatation is found in the first pregnancy, and there is a tendency toward decrease of size of dilatation in each succeeding pregnancy. Although the "hydroureter of pregnancy" depends on the endocrine function of the placenta, it was impossible with estrogens, in the amounts used, to reduce existing dilatation in late pregnancy or to speed up postparturitional regression, nor was premature dilatation induced with progesterone.

Van Wagenen and Jenkins conclude that physiologic hydroureter of pregnancy is dependent primarily on the preservation of the endocrine functions of the placenta. There appears to be no definite progressive injury to the ureter as a result of repeated pregnancy. The dilatation is of greatest size in the first pregnancy, and there is a definite tendency to decrease in each succeeding pregnancy. If such conditions exist in man, infection should be less frequent after the first pregnancy. The estrogens and progesterone failed, in the amounts used, to influence dilatation.

MacLean and Deming¹⁷ state that the incidence of pyelonephritis in pregnancy diminishes with each successive pregnancy. Two thirds of all the infections occurred in the first and second pregnancies. The incidence of infection increases each

16 van Wagenen, G, and Jenkins, R H. Pyelo-Ureteral Dilatation in Successive Pregnancies, *J Urol* 49 228-235 (Feb) 1943

17 MacLean, J T, and Deming, C L. The Incidence of Pyelonephritis in Successive Pregnancies, *J Urol* 49 236-241 (Feb) 1943

month, with the maximal occurrence at the fifth and sixth months of pregnancy. This parallels the incidence of occurrence of dilatation of the ureter. Both parallel exactly the increased excretion of estrogen and corpus luteum hormone by the placenta during pregnancy.

Bacilli of the colon group were the commonest infecting organisms, and staphylococci the next commonest. The bacteria from cultures agreed with those of stained smears in 72 per cent of the cases. The bacteriology of bacillary infections, including a review of the literature, has been reported by Sandholzer and Scott.

Pyogenic infection of the urinary tract occurring during pregnancy is not, in MacLean and Deming's opinion, an indication per se for abortion. There is no association between the month of pregnancy at which the infection occurs and the ability to reach term, provided that conservative treatment is used. By using conservative treatment, 85 per cent of the patients were carried to term or until the fetus became viable, and of these 90 per cent were delivered of living babies.

That pyelitis practically never exists without pyelonephritis is accepted as established. In MacLean and Deming's experience, a considerably reduced excretion of phenolsulfonphthalein is absolute evidence of pyelonephritis.

The incidence of hypertension in the group of infections associated with pregnancy was 27 per cent and no higher than that which occurred in any group of cases of pyelonephritis not complicated by pregnancy.

An acute infection of the upper part of the respiratory tract immediately preceded the onset of the urinary infection in many of the cases. Dilatation of the ureter was likewise a common finding.

Mandelic acid and the sulfonamide compounds were found to be the most effective drugs in combating urinary infection. The range of organisms for which they were effective was greater than that of any other single drug used.

Irrespective of the month of onset of the infection, treatment was given until the patient was either "cured" at term or delivered. In only 25 per cent of the cases were the patients "cured" at term, yet within two weeks of emptying the uterus, 90 per cent of the patients were asymptomatic and free of infection.

URETER

Stone—Kastner¹⁸ recommends the vaginal removal of ureteral stones which are in the lower end of the ureter. In cases of a palpable stone the operation is not very difficult. Kastner stresses the importance of careful suture of the ureter after removal of the stone. In those cases in which there is considerable infection of the urinary tract, this operation should not be carried out, as it fairly commonly results in the formation of a ureterovaginal fistula. In suitable cases Kastner covers the ureteral suture with a fatty fascial flap.

Dilatation—Leyh¹⁹ discusses gigantic dilatation of the ureter and reviews the development of the normal ureter. In most cases dilatation of the ureter arises from mechanical or functional disturbance of the outflow as well as by abnormal development. Precise discrimination between secondary dilatation and the true gigantic ureter or megaloureter is sometimes difficult to make. In order to make the diagnosis of megaloureter, definite changes in the ureter itself must be found, such as irregularity in the construction of the ureteral wall (fusiform or segmental forms), hypertrophy of the muscularis and simultaneous dilatation of the lumen and a marked increase of the connective tissue elements.

18 Kastner, H. Zur vaginalen Ureterotomie, *Ztschr f urol Chir u Gynak* 46 111-116, 1941.

19 Leyh, K. Ueber den Riesenharnleiter und seine Entstehung, *Ztschr f Urol* 36 37-60, 1942.

Leyh reports 5 cases of megaloureter and concludes that the hypothesis of Bard is the most probable one—that as a result of a congenital weakness of the ureteral wall the ureter cannot resist the normal or physiologic pressure of the outflowing urine, the result being an early dilatation and hypertrophy of the wall. The fact that one often finds other abnormalities, such as hypospadias, phimosis and anomalous types of kidneys, in association with megaloureter suggests the embryonal origin of that condition.

Intubated Ureterotomy—Davis²⁰ discusses a new operative procedure for ureteral and ureteropelvic stricture—intubated ureterotomy. His work on this subject was prompted by the results in a case of urethral stricture. After the scarred, diseased tissue was laboriously dissected away, there were left a huge hole in the perineum and a narrow ribbon of urethral wall, representing a part of the roof of that organ, bridging a gap in the urethra a good $1\frac{1}{4}$ inches (3.2 cm) long. A catheter was left in the urethra, after which the urethral mucosa spread around the catheter and completely filled in the gap.

Davis applied this same principle in 5 cases of ureteral stricture which he reports.

In the first case a stricture was found in the upper part of the ureter, which was cut through in an effort to obtain a small stone in the kidney. A no. 12 rubber catheter was brought down through the nephrotomy opening into the ureter. The ureter was closed loosely about the catheter, but a considerable defect remained at the point of the stricture. The catheter was left in for two weeks. Later it was found that the persistent narrowing in the upper part of the ureter was entirely obliterated and the patient did not have any further pain in his kidney.

In the second case the patient had a stone which extended into the ureteropelvic juncture. At operation the ureter was found encased in a thick mass of fat. The ureter was definitely narrowed below the kidney. A rubber tube was passed down the ureter 10 cm and brought out through a small nephrotomy incision. No ureteral sutures were used, and the tube was exposed in the ureterotomy opening. The tube was removed accidentally on the tenth day, but the wound healed without trouble. A month later the patient was well.

In the third case there was a marked stenotic area just below the ureteropelvic juncture. A no. 12 bulb could just be forced through the strictured area. The ureter was incised longitudinally over a larger bulb, and a rubber tube, no. 14 F, was passed down below the area of incision in the ureter. A large portion of the tube was exposed and the ureter was not closed over this. The incision healed by first intention around the tube. A study of later roentgenograms showed a good result.

The remaining 2 cases were somewhat similar, unbridged areas in the ureter being left without sutures and good results being obtained.

In intubated ureterotomy, no effort is made to draw the tissues into a new form, and no sutures are used. The operation depends on the physiologic repair processes of the tissues. The splint is a mold on which the tissues, by their own proliferation, reform the ureteral channel in normal size and shape. It must be left in place, therefore, until this proliferation is completed and the new channel is lined by epithelium.

In the use of a ureteral or ureteropelvic splint, the size of the splint, its shape and the length of time it is left in place are the most important points. Davis believes that many tubes used as splints have been too small. It seems reasonable

20 Davis, D. M. Intubated Ureterotomy. A New Operation for Ureteral and Uteropelvic Stricture, Surg. Gynec. & Obst. 76: 513-523 (May) 1943.

that a tube used for this purpose should be as large as will enter the uncut or presumably normal, part of the ureter without fitting so tightly as to cause ischemia of its wall. It may well be that specially shaped splints, including perhaps conical ones for the ureteropelvic junction, will prove to be useful. If a splint is withdrawn too soon, it will fail of its purpose. The allowance of time for the tissues to reconstruct themselves about it should be generous, erring on the side of too long rather than on the side of too short. Three weeks may be enough but should be regarded as a minimum. It will seldom be necessary to leave a splint in place more than four or five weeks.

Ureteral Transplantation—Reimers²¹ discusses the question of ureteral transplantation. He states that the mortality rate is extremely high. In the review of 1,360 cases in which operation was performed, he found 348 deaths (26 per cent). More than 60 per cent of the deaths were due to ascending infection of the kidneys following operation, 30 per cent were due to postoperative peritonitis.

Reimers reports a series of experimental transplantations in 150 dogs. He states that the results are much more satisfactory in human beings than in dogs and gives the combined results of his animal experimentation and his clinical cases.

The peritonitis does not result from an imperfection of technique but from an unavoidable biologic process, that is, transverse section of the ureter results in necrosis of the stump, which may vary from a few millimeters to several centimeters and which in some cases may even involve the intraperitoneal part of the ureter. This necrosis of the stump is not caused by disturbance of the circulation but is secondary to a necrotic inflammation caused by the intestinal bacteria. The necrosis is also increased by the retraction of the ureteral stump which results from peristalsis. The necrosis also initiates the ascending renal infection. The necrosis of the ureter also causes ureteral obstruction, and three to five days after the operation one usually finds that there are hydronephrosis and ascending pyelonephritis, which may be followed by uremia and death. Reimers advises splinting of the anastomosis with a ureteral catheter in some cases, although he states that this may cause an early incrustation and blocking of the ureter especially in the presence of infection. In some cases nephrostomy or pyelostomy may be advisable to prevent these complications. In the majority of cases good results are obtained at the onset, but a cicatrization of the outlet may develop, especially when the necrotic stump of the ureter sloughs off inside the oblique channel.

Reimers discusses his own method of ureteral transplantation. The ureter is implanted in the shortest possible way, and the oblique channel method is not used. He plants the ureteral stump in the intestinal wall between the muscularis and the mucosa and surrounds it by a thin ring of nonoxidizable steel wire. The wound is covered by a peritoneal flap. Later the ureter is cut through by means of the steel wire through the resectoscope, with an electric cautery. The opening from the ureter is also increased by the use of a specially constructed pair of scissors through the resectoscope.

BLADDER

Tumor—Abeshouse²² collected records of 26 cases of carcinoma in exstrophy of the bladder and added 1 personal case. Adenocarcinoma was the type of tumor encountered in 21 of the 27 cases.

21 Reimers, C. Das Problem der Harnleiterverpflanzung in den Darm, *Ztschr f urol Chir u Gynäk* 46 71-110, 1941.

22 Abeshouse, B. S. Exstrophy of the Bladder Complicated by Adenocarcinoma of the Bladder and Renal Calculi, *J Urol* 49 259-289 (Feb) 1943.

Exstrophy of the bladder and epispadias can be best explained on the basis of defective embryonic development. The most satisfactory explanation is that exstrophy is caused by mesodermal deficiencies resulting from faulty development of the mesodermal mass which originates from the caudal margin of the embryonic shield and the caudal end of the primitive streak and gives rise to the ventral abdominal wall, genital papilla, symphysis pubis and muscular coat of the bladder.

The best results in the treatment of exstrophy of the bladder are obtained by transplantation of the ureters to the rectum combined with excision of the exstrophied bladder.

There is much histologic evidence to show that the mucosa of the normally developed and exstrophic bladder may undergo metaplastic changes as a result of chronic inflammation, irritation or obstruction.

Cystitis cystica and cystitis glandularis develop by a process of metaplasia of the epithelium of the bladder which passes through successive stages, that is, cell nests of Brunner, cystitis cystica and cystitis glandularis. The formation of lumens and glandular elements within the cell nests appears to involve an active secretory process rather than a degeneration of the central cells.

Cystitis cystica and cystitis glandularis are relatively common lesions but are frequently overlooked or not recognized by the cystoscopist or pathologist. They are benign lesions but must be considered potentially malignant, for they serve as the origin of adenocarcinoma in the normally located or the exstrophic bladder in a manner analogous to the development of squamous cell carcinoma from leukoplakia.

There is little evidence to support the contention that adenocarcinoma of the normally situated or exstrophic bladder is due to embryonal displacement of cloacal or intestinal epithelium, except in cases of tumors in the urachal area of the bladder.

Sumner and Gaynor²³ report 2 cases of adenocarcinoma of the bladder. Various hypotheses in regard to their origin have been discussed. The first case is best explained by an error of embryologic development or association with the urachus. In the second case the lesion, because of its location on the trigone, might be the result of metaplasia or a proliferation of aberrant glands, but an origin similar to that in the first case is also possible.

Kirwin²⁴ states that vesical papillomatosis is the term applied to a condition of the bladder wherein multiple papillomas appear on the mucosa. Histologically it does not differ from solitary growth of the same structure.

Though recognized clinically for more than a century, papilloma of the bladder was regarded as primarily malignant and seldom cured until early in the twentieth century, when the high frequency current gave a treatment which produced some clinical cures, though it yet was far from entirely satisfactory.

Kirwin believes that vesical papillomatosis is due to a virus. His hypothesis has received support and confirmation in the work of Wile and Kingery on the etiology of common warts and the more recent demonstration of Beard and his co-workers at Duke University that a "specific material" exhibiting the biologic characteristics of the virus responsible for rabbit papilloma could be obtained from extracts made from the growths themselves.

In accordance with this conception, Kirwin undertook the treatment of vesical papillomatosis in 4 cases by excision of the growths with the wire loop electrode.

23 Sumner, W. A., and Gaynor, E. P. Goblet-Cell Adenocarcinoma of the Urinary Bladder. Report of Two Cases, *J Urol* 49 419-425 (March) 1943.

24 Kirwin, T. J. Papillomatosis of the Bladder. New Conceptions of Etiology and Treatment. *J Urol* 49 1-13 (Jan) 1943.

cauterization of the bases with the ball electrode and sterilization of the mucosa of the bladder by application of a 50 per cent solution of phenol in glycerin, followed by 95 per cent alcohol, when the solution of phenol has been in contact with the mucosa for about three minutes

In a discussion of carcinoma of the bladder and the importance of recto-abdominal palpation with the patient under anesthesia in the selection of cases for total cystectomy, Jewett²⁵ states that during the past two years he has carried out ureteral transplantation on 31 patients, 26 of whom had extensive cancer of the bladder. The majority of these 26 patients had been under conservative treatment elsewhere for many months, sometimes years, before they were referred for cystectomy. In 15 cases he was impressed with the fact that palpation of the bladder from within the peritoneal cavity at laparotomy revealed a much larger tumor than had been suspected on cystoscopic examination. The second stage of this operation has been carried out in 20 cases, but has been combined with cystectomy in only 16.

In 4 of the series of 26 cases of extensive carcinoma of the bladder the condition was found to be inoperable at laparotomy, and in 4 others recurrence or metastasis developed after cystectomy. It is apparent, therefore, that the usual methods of examination are inadequate to establish operability.

For practical purposes it is necessary to have a simple working classification which is based on the answer to the two most important questions of all: 1. Has the tumor invaded the bladder muscle? 2. Is it operable? For determining the most appropriate treatment, Jewett separates tumors of the bladder into three groups.

Group 1 includes the noninfiltrating tumors. Cystoscopic examination establishes the diagnosis for this group. If, however, the intravesical mass is large and its base not well visualized, so that the possibility of infiltration cannot be excluded, subsequent rectoabdominal palpation with the patient under intravenous or spinal anesthesia should be carried out, usually just before endovesical destruction of the tumor.

Group 2 is made up of infiltrating tumors completely confined to the wall of the bladder. If in the absence of marked vesical symptoms cystoscopy should be undertaken with the patient under local anesthesia, the appearance of the tumor and the surrounding vesical mucosa will suggest at least some infiltration. A subsequent examination with the patient under intravenous or spinal anesthesia is then indicated for the purpose of making a more accurate inspection, obtaining a specimen for a biopsy and making a bimanual examination.

Group 3 is made up of infiltrating tumors with perivesical extension, with or without metastasis. A cure by total cystectomy in the majority of cases in this group is impossible. Inoperability is indicated by any one of the following findings: (1) a large, hard, irregular mass projecting well beyond the wall of the bladder which sometimes can be felt also by the fingers palpating the abdomen, (2) thickening and induration in the inferolateral ligaments of the bladder when the tumor involves the base, (3) fixation of the mass to the bony pelvis or to other perivesical structures, unless these are structures which can be completely removed with the bladder, such as the seminal vesicles or the upper part of the vagina in women,

²⁵ Jewett, H. J. Carcinoma of the Bladder. The Importance of Recto-Abdominal Palpation Under Anesthesia in the Selection of Cases for Total Cystectomy, *J. Urol.* **49**: 34-41 (Jan.) 1943.

(4) metastasis, which may be revealed by general physical examination and roentgenograms of the thorax, spinal column and pelvis

Jewett concludes that rectoabdominal palpation while the patient is under anesthesia is the most satisfactory method for determining whether the primary carcinoma is confined to the wall of the bladder. It is practicable and is indicated as a routine procedure in all cases of tumor of the bladder in which there is any question of infiltration, as revealed by cystoscopy and biopsy. Total cystectomy as a means of cure should be considered only when the mass is completely confined to the bladder wall and is movable. Rectoabdominal palpation with the patient under anesthesia in cases of carcinoma of the bladder gives invaluable aid in establishing two facts: (1) deep invasion of the bladder muscle, indicating the probable hopelessness of further conservative management, and (2) suitability of the case for radical cure by total cystectomy.

Vesicointestinal Fistula—Lazarus and Marks²⁶ state that vesicointestinal fistulas may be divided into actual fistulas and incipient or threatened fistulas.

Analysis of the literature indicates that inflammatory lesions of the bowel constitute the underlying cause of fistulas in 51 per cent of cases. Tumors of the bowel were present in 21.3 per cent of the collected cases. A review of cases of intestinal inflammation shows that diverticulitis was the primary cause in 65.8 per cent. The most frequent neoplastic lesion of the bowel was carcinoma of the rectum (50.8 per cent). As regards the location of the fistula, it was noted that the most frequent site was between the bladder and the rectum (43.5 per cent).

The cardinal symptom of actual fistula is the passage of gas or feces through the urethra. Symptoms of an incipient or threatened fistula are more suggestive than pathognomonic. In cases in which the primary lesion is in the bladder, the appearance of intestinal symptoms is suggestive of a contact inflammation between the bladder and the intestine. When the primary lesion is in the bowel, the appearance of vesical symptoms should likewise suggest this same condition.

Diagnosis, especially in cases of incipient fistulas, depends primarily on cystoscopic examination.

Proper preoperative preparation of the bowel is probably one of the most important requirements for successful surgical intervention. In cases of actual fistulas, graded stage operations are necessary. The use of an indwelling urethral catheter obviates the necessity of closing the fistulous opening in the bladder. Systemic and local employment of sulfonamide compounds has been found of great value.

Prognosis depends entirely on the underlying pathologic condition.

Rupture—Bacon²⁷ reports a series of 147 cases of rupture of the urinary bladder. The predominating symptoms and findings were pain, shock, hematuria, retention of urine and skeletal injuries. Cystography was the most significant single diagnostic procedure. Ideal management consisted of immediate treatment for shock, early diagnosis, prompt surgical exploration and suprapubic cystostomy. The total mortality rate was 44.2 per cent (65 deaths), and the surgical mortality rate in the 126 cases in which operation was performed was 36.5 per cent (46 deaths).

26 Lazarus, I. A., and Marks, M. S. Vesico-Intestinal Fistula—Actual and Incipient Early Diagnosis and Treatment, *Am J Surg* 59:526-535 (March) 1943.

27 Bacon, S. K. Rupture of the Urinary Bladder. Clinical Analysis of One Hundred and Forty-Seven Cases in the Past Ten Years, *J Urol* 49:432-435 (March) 1943.

Radiation Injuries—Kulitz²⁸ carried out systematic urologic examinations in 150 cases of carcinoma of the uterus. Damage to the bladder following roentgen and radium therapy frequently causes conditions which are similar to the radiation injuries of the skin. He distinguishes several stages. In the first place these patients get acute cystitis with frequency of urination, dysuria and tenesmus. At cystoscopy, hyperemia is found. In an occasional case there are also ulceration and necrosis of the wall of the bladder. This condition usually starts one or two weeks after the first application and is due primarily to a large, initial dose, especially in the cases in which radium is used. There is also a secondary chronic lesion which results from the cumulative effects of a series of radiation treatments. In these cases, cystoscopy reveals telangiectasis with capillary aneurysms together with atrophy of the mucosa of the bladder. This condition may cause hematuria together with chronic ulceration. These secondary changes develop from one month to several years after the first irradiation. Radium treatment most commonly causes changes in the base of the bladder and in the region of the trigone. Lesions occurring in the vertex most commonly result from roentgen therapy. There is also a third group of injuries which are caused by radiation therapy plus some other traumatic factor, thermal, mechanical, chemical or infectious.

Malacoplakia—Ledergerber²⁹ states that malacoplakia is rarely encountered in the living patient. He reports a case of this condition in a woman aged 39 years who had had repeated attacks of cystopyelitis over a period of ten years. These attacks lasted for several weeks and were usually associated with severe pain in the left renal region. The urine showed evidence of infection. The tests of renal function gave normal results. On cystoscopic examination the vesical mucosa showed a number of irregularly disseminated circular foci of different size with pale red, raised regions. Biopsy of one of the regions showed malacoplakia. The regions were covered by normal mucosa and were composed of a mass of granulations formed of round and oval epithelial cells. There were also infiltration of pus cells and many capillary vessels. A second cystoscopy, three months later, showed only a few of these regions in a comparatively normal bladder. Infection with *Escherichia coli*, which was found at the first examination, was still present, though not so severe. Ledergerber states that malacoplakia seems to be a special form of reaction of the mucosa of the urinary tract in cases of severe infection with *Escherichia coli*. This apparently is in evidence for only a short period and then changes over to a form of cystitis granularis. A few cases which have been observed in vitro and reported in the literature confirm these statements.

Neurogenic Conditions—Smith and Strasberg³⁰ state that it is the common belief that dilatation of the ureter and renal pelvis accompanies the neurogenic and the cord bladder. They carried out a series of studies of the innervation of the ureter. These dissections demonstrated a relative lack of nerve fibers to the middle three fifths of the ureter, as contrasted with the terminal portions. Cystometrographic studies revealed that the earliest manifestation of syphilitic involvement of the nervous system is to be found in the nerve mechanism of the bladder. Smith and Strasberg investigated 50 cases of neurogenic and cord bladder and did not encounter a single case of dilatation of the ureter and renal pelvis. Tests of renal function did not demonstrate any impairment of function.

28 Kulitz, G. Die Strahlenschädigung der Blase. *Ztschr f urol Chir u Gynäk* 46 125-134, 1941.

29 Ledergerber, E. Ein Fall von Malakoplakie der Harnblase, *Ztschr f urol Chir u Gynäk* 46 139-142, 1941.

30 Smith, E., and Strasberg, A. The Upper Urinary Tract in Cases of Neurogenic Bladder. Preliminary Communication. *Tr Am A Genito-Urin Surgeons* 35 147-152 1942.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1942

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN
ACADEMY OF ORTHOPAEDIC SURGEONS

XIV CONDITIONS OF THE FOOT AND ANKLE

PREPARED BY EMIL D W HAUSER, MD, CHICAGO

ASSISTED BY ROBERT MONTGOMERY, MD, MILWAUKEE

According to Selig,³⁶⁸ the basic pathologic process of common painful lesions of the foot is a compression of the soft parts, the skin and subcutaneous tissue between underlying bony prominences and the leather of the shoe or another bony prominence. The result is thickening of the skin, formation of a bursa and eventually cartilaginous and later bony proliferation at the points of pressure. He feels that relief should be obtained by wearing of well fitting shoes or by surgical removal of the underlying protuberance.

[ED NOTE—The conditions mentioned, namely, bursitis, calluses and corns are not basic but are symptomatic. It is malposition of the structures of the foot that makes the foot vulnerable to the contact of the shoe. This malposition of the foot has to be traced to its cause. The treatment as outlined by Selig is symptomatic that is, its principle is that the friction must be relieved by altering the shoe so that it cannot press on the structures. Selig's recommendations for symptomatic treatment of the different conditions are useful, but the conditions must be corrected more basically by reestablishing normal position of the foot and normal function.]

Lake³⁶⁹ makes an appeal for the influence of structural changes that are based on heredity and are traced back to faulty development in the course of evolution. He states that "a well developed foot judged by evolutionary criteria, may stand up to considerable abuse, failing only when the mal-treatment becomes excessive but a badly adjusted foot may fail under normal stresses of ordinary locomotion without any misuse whatsoever."

Morton³⁷⁰ wishes to distinguish between the signs of a faulty shoe and those of internal disorders of the foot and suggests that one can assume that pain on the top and sides of the foot is due to a faulty shoe but that when the disorder is on the bottom or sole of the foot the trouble is probably in the foot. He emphasizes roentgen studies for the diagnosis of disorders within the foot. He believes that the symptoms are due to irritation and therefore recommends plenty of rest.

Osgood³⁷¹ gives a historical review of the scientific investigations of the foot with special reference to the work of Duchenne, who demonstrated the imbalance between the inverter and the everter muscles of the foot in foot strain. In 1907 the author and Dr. Legg carried out an experiment to establish the strength of the two groups of muscles and were able to demonstrate "In the first group which one may call the symptomless normal feet, the inverters of the foot acting as

368 Selig S. Painful Lesions of Feet. Their Basic Pathology and Treatment. *J Mt Sinai Hosp* 8 1216-1219 (March-April) 1942

369 Lake, N C. Evolution as Etiologic Factor in Foot Disorders (Bolingbroke Lecture). *Brit M J* 1 31-35 (Jan 10) 1942

370 Morton, D J. Functional Disorders of Feet and Their Treatment. New York State J Med 42 2119-2123 (Nov 15) 1942

371 Osgood R B. Important Etiologic Factor in So-Called "Foot Strain" (Faulty Muscle Balance), *New England J Med* 226 552-557 (April 2) 1942

protectors of the arches, were stronger than the everters or depressors of the arches in the ratio of approximately 5 pounds pull of the inverting protectors to 4 pounds pull of the everting depressors. In the third group, that of patients with more pronated feet seeking advice because of symptoms of foot strain, the pounds pull of the everters or depressors of the arches was definitely stronger than that of the inverters or protectors of the arches." On the basis of these experiments, they carried out exercises which increased the strength of the inverters, or protectors of the arch, with good results. He speaks of the difficulty of getting a patient to carry out the exercises.

[ED NOTE—The imbalance of muscles cannot be assumed to be primary. It is true that the inverters in cases of foot strain and of pes valgoplanus are proportionately decreased in strength while the everters are increased. It is necessary to establish the cause of the imbalance. It is known that a foot that is totally decompensated will go into valgus position, and the continuous use of the foot in the valgus position is bound to increase the strength of the everters and proportionately decrease the strength of the inverters. The results obtained by reestablishing the normal balance between the inverters and the everters will in turn reestablish the normal position of the foot, but it has been the experience of one of the editors (E D W H) that it is more practical to bring the foot into normal position and then carry out normal functional exercise, namely, correct gait, in order to obtain the results mentioned by Osgood.]

According to Hauser,³⁷² most common disorders of the foot are due to functional decompensation. Functional decompensation is an imbalance between the demand made on the foot and the capacity of the foot to do the work required of it. This imbalance may be due either to an increase in load or to a decrease in strength. A functional decompensation of the foot, like a cardiac decompensation, will give rise to a definite symptom complex and objective findings, such as fatigue, some stiffness, tenderness, overstrained ligaments, muscle spasm and contractures, valgus deformity of the heel, pronation in the midtarsal area, abduction of the anterior part of the foot and lowering of the longitudinal arch. The head of the first metatarsal is forced dorsally and away from the second, the fifth metatarsal is similarly spread away from the fourth, there are flexion contracture of the toes with secondary clavi, hallux valgus deformities of the great toes and accompanying bursitis, periostitis, and in some cases spur formation at the attachment of the plantar fascia to the calcaneus.

Correction requires reestablishment of normal relationship of the bones and relief of functional decompensation. To accomplish this, the heel of the shoe is raised on the inner side, forming an inclined plane which brings the heel of the foot into varus. The distorted anterior part of the foot is corrected and brought into normal relationship with the varus position of the heel by a comma-shaped bar that is higher on the outer side forming an inclined plane that is higher under the fourth, third and second metatarsal bones than under the first. It does not go under the fifth, because this is normally weight bearing and is relatively lower than the middle three. The distance from the bar to the heel must be sufficient to allow pliability in the region of the shank of the shoe. The pliability of the leather in the sole permits the heel to be twisted in one direction while the transverse bar forces the anterior part of the foot in the opposite direction. With the correction of the valgus of the heel and the anterior supination in the manner described, the longitudinal arch is restored, as is also the anterior, or transverse, arch (correction

³⁷² Hauser, E. D. W. Common Disorders of Foot. Quart. Bull., Northwestern Univ. M. School 16:110-113, 1942.

of pes latus) The reestablishment of the normal position of the head of the first metatarsal bone tends to straighten the great toe (decrease of hallux valgus) The raised comma-shaped bar stretches the muscles of the toes with each step and straightens out the contracted toes Bringing the heel into varus and the anterior part of the foot into relative pronation relieves the tension on the plantar fascia and permits the periostitis to subside If the deformities are mild or moderate, this conservative treatment will be sufficient to cure them The corrective shoe permits and encourages the establishment of the normal anatomic relationship of the bones to each other and reestablishes the propulsive force, thus normal function is made possible The patient is taught how to walk properly, in a heel and toe manner

Hamsa³⁷³ urges interest on the part of the medical profession in the treatment of common disorders of the foot He speaks of the local treatment with regard to good shoes and stockings that fit He discusses his method of treatment for pes valgoplanus, in which he raises the inner side of the heel and the outer side of the sole of the shoe, and advises special exercises to increase the strength In speaking of the soft corn, he refers to the fact that many such lesions are complicated by fungous infection He treats the fungous infection and uses a pad to prevent friction rub, and in certain cases he advises the removal of the bony prominence beneath the corn In the treatment of disorders of the foot he stresses a general systemic examination

According to Hale,³⁷⁴ people who wear no shoes or wear a Munson last have good feet from a functional point of view, the average custom-made shoe has a tendency to cause a lateral deviation of the big toe and the anterior part of the foot, together with a compression of the anterior part of the foot This deviation of the anterior part of the foot causes a partial or total loss of support of the head of the first metatarsal bone With regard to the symptoms of foot strain, he also brings out that there is a tendency toward tightness of the hamstring muscles and inability fully to extend the knee, as well as an overdevelopment of the muscles of the outer part of the calf and the thigh He feels that with treatment 100 per cent of the disorders of the foot resulting from wearing improper shoes should be prevented In his opinion properly built and properly fitted shoes and normal walking will correct the disorders in young people that have been present as a result of bad shoes, as to those of older people, he is not optimistic

[ED NOTE—It is our experience that deformities of the foot can develop in people who go barefoot The natives who were the subjects of early studies were apparently warriors and people in excellent physical condition According to the observations of one of the editors (E D W H) primitive races that show signs of general physical degeneration show also pes valgoplanus and other deformities of the foot]

In this article Chandler³⁷⁵ brings out the fact that pronated feet in children result from inadequate ligamentous tone of primary or secondary origin It is unreasonable to expect the tarsal structures to exhibit degrees of tone differing from that found in similar structures elsewhere in the body Pronated feet are the rule in the presence of general muscular or ligamentous hypotonia of any origin Examples are commonplace in rickets, amyotonia, arachnodactyly, congenital heart disease and malnutrition and after any prolonged illness Pronated feet of secondary origin reflect some basic imbalance of muscular action The treat-

373 Hamsa, W R Treatment of Common Foot Disorders, Nebraska M J 27 242-245 (July) 1942

374 Hale, T, Jr Cause and Prevention of Weak Feet, Mil Surgeon 90 518-535 (May) 1942

375 Chandler, F A Children's Feet, Normal and Presenting Common Abnormalities, Am J Dis Child 63 1136-1146 (June) 1942

ment or pronated feet consists in the restoration of muscle and ligamentous tone by the elimination of the causative factors. It must be general as well as local. Exercises should be directed toward the strengthening of flexor muscles acting on the toes and flexor muscles of the forefoot. Stretching of the calf muscles should always accompany exercises directed toward increasing their strength. The use of molded foot plates or the prolonged use of plaster casts is rarely if ever indicated. Shoes of substantial construction are essential. These should be altered so as to move the center of weight bearing laterally, restoring the normal bony relations in the feet. Operative measures are indicated only in cases in which the condition is persistent. In addition, there are diagrammatic drawings and photographs. Some of the photographs show the form of exercises that he recommends.

Thelander and Fitzhugh³⁷⁶ made a thorough study in which they made the following observations. Deviations from the ideal midposition of children's feet may be partly due to prenatal causes and partly acquired by faulty sleeping positions. Some of these malalignments are actual and persist, and others may disappear during normal growth under favorable conditions of symmetric activity. It is important that deviations from the neutral position be recognized and corrected before weight bearing begins. Sleeping and sitting in distorted positions during infancy and childhood are found to cause permanent distortions of the feet, ankles and knees. It is not safe to assume that all early faults in alignment will automatically disappear during the period of growth. The earlier a distortion and its contributing factors are recognized and measures taken to overcome them, the more certain are the results.

[ED NOTE—This is a good study and confirms the observation of others, but it is the first time it has been recorded as a scientific study, namely, that there is a variation in the feet of children at birth and in the subsequent growth before weight bearing. This variation has been considered within the range of normal as long as it was not necessary to bring about mechanical interference, so that the distinguishing line between a true pes adductus and a foot with inversion tendency is sometimes difficult to determine. The relationship of the child's posture in sleeping, sitting and crawling and the position of the foot before walking are worthy of attention.]

Wood³⁷⁷ states that in the terminology of medical category sheets the foot troubles fall into three main groups: severe, moderate and minor. At Horton Hospital an outpatient foot clinic has been instituted. Persons with disorders of the feet are sorted into two groups: (1) those needing inpatient treatment, (a) remedial exercises, (b) manipulation or (c) operation (with an unwilling patient surgical intervention may do more harm than good), and (2) those who can be treated as outpatients. In general, it has been found better not to hospitalize soldiers for more than three weeks, because of complications arising in regard to movements of troop units. In the outpatient groups are those who can be benefited by simple expedients. Boots are carefully fitted, socks are inspected for shrinkage, and wedges or insoles are made or fitted. The use of a valgus insole or a metatarsal bar has proved practical. An outside bar wears out so rapidly that an inside sponge rubber pad is preferable.

According to Crisp,³⁷⁸ only a minority of soldiers with painful feet show glaring defects. He divides the men with disorder of the feet into two groups: those

376 Thelander, H. E., and Fitzhugh, M. L. Posture Habits in Infancy Affecting Foot and Leg Alignments, *J. Pediat.* **21** 306-314 (Sept.) 1942.

377 Wood, H. L. C. Foot Problem in Service Cases, *Proc. Roy. Soc. Med.* **35** 193-195 (Jan.) 1942.

378 Crisp, E. I. Physiotherapy and Soldier's Foot, *Proc. Roy. Soc. Med.* **35** 217-220 (Jan.) 1942.

who had no trouble prior to entering the army, and those who had trouble before their entrance. The men that did have trouble before joining the army he groups again into those with weak feet, those with stiff feet and those with incoordinated feet. The weak foot requires six to eight weeks of treatment, including application of heat, massage and exercises. For the stiff foot, the prognosis following similar treatment plus manipulation is excellent. The incoordinated foot under military training becomes still more incoordinated, which may result in the development of deformity. After preliminary rest in bed, the keynote of treatment is to develop disassociation of the tibialis anticus and extensor digitorum longus muscles. This is accomplished through training of the muscles and stimulation of them by "surging" taradism. Feet which were troublesome in civil life are often aggravated by the military requirements.

Cozen³⁷⁹ advises that frequent reexaminations be made to eliminate those rare persons having the early symptoms of thromboangitis obliterans (Buerger's disease), arthritis and march foot. A medical officer will find that many forms of therapy for treating the same condition of the foot must be known to him, inasmuch as one method is not universally obtainable or applicable in the army. He points out that the pain of flatfoot, when the origin is largely based on a soldier's discontent with his duties or environment, will not be relieved by the medical officer.

As a prophylactic measure Rostrup³⁸⁰ advises a careful inspection of the feet at the time of recruiting as most important from the point of view of economy and efficiency, and gradual early training to break in a new recruit and not break down his feet. He recommends the teaching of foot hygiene to the platoon officers and men. He stresses the importance of the treatment of minor conditions of the feet, such as blisters, to prevent more serious conditions. The experiences with surgical operations on the feet in rehabilitating soldiers has not been fortunate, and for this reason major disabilities will have to be assessed and treated if indicated along conservative lines. Operation, at present, should be allowed only in selected cases and then its value in the Army is open to doubt.

Barry³⁸¹ emphasizes the importance of the foot for all three branches of military service. He has followed men who were discharged from the Air Force because of foot disabilities after completing their training and he brings out the point that some of these disabilities should have been recognized earlier, to save the tremendous expense of training the men. He has found that men with severe conditions, like tumors and changes that can easily be recognized by roentgen examination, are adequately rejected. There are a number of borderline types of disabilities of the foot which he describes and details are given for the standards of acceptance or rejection.

[ED NOTE—The difficulty arises not in recognition of the anatomic changes but in the variation of the functional capacity, and in addition to the observation of the alterations that are seen in the feet one must take into consideration the functional capacity that the man was subjected to during his civilian life. This is a further aid in judging capacity to carry out the military demands and is of value in the selection or rejection of these military candidates.]

379 Cozen, L. N. Treatment of Painful Feet in the Army, *Mil Surgeon* **91** 196-198 (Aug.) 1942.

380 Rostrup, O. Inspection and Treatment of Soldier's Feet, *Canad M A J* **47** 323-326 (Oct.) 1942.

381 Barry, D. Foot Standards for War Service *M J Australia* **1** 404-406 (April 4) 1942.

In a true giant growth of the foot Bergmann³⁸² offers an improvement in treatment by removal of the fifth toe and the fifth metatarsal bone and partial excision of the cuboid bone. The tendon of the peroneus brevis muscle was reanchored on the cuboid bone. He found that there was no interference with function and there was an improved cosmetic result.

Wagner³⁸³ reports the results of 100 cases in which he did a calcaneocuboid arthrodesis and performed arthrodesis on the subastragaloid joint. In addition, he constructed an anatomic elongation on the posterior aspect of the astragalus by means of a reflected segment of the os calcis. This piece of bone articulated with the inferior posterior surface of the tibia. In other words, this is a modified Campbell bone block. He reported good results except in 8 cases in which there was a varus deformity, which deformity he counteracted by dividing the tibialis posticus tendon, 1 case in which revision of the height of the transplanted bone was made to allow more extension of the foot, 1 case of bilateral spastic equinus due to encephalitis in which the patient died and 20 cases in which there was some difficulty in healing of the posterior wound. All healed within three months.

[ED NOTE—In the opinion of one editor (E D W H) it is preferable to perform the triple arthrodesis along with the posterior bone block. In many cases it is well to correct the deformity, if there is one present, by means of manipulation before doing the arthrodesis, inasmuch as it gives a longer and more stable foot and requires less removal of bone structures.]

For the surgical correction of pronated feet due to loss of support by the deltoid ligament, Milch³⁸⁴ describes the following operation. A tunnel, running antero-posteriorly, is made, beginning on the medial surface of the tibia, above the epiphysal line. Through this a guide suture is passed. The incision is opened so as to expose the abductor hallucis muscle below and the tendon of the tibialis posticus muscle in front. The sustentaculum tali is visualized between the tendon of the tibialis posticus and that of the flexor digitorum longus muscle. With a broad, blunt periosteal elevator, all the tissues lying below the sustentaculum and posterior to the calcaneocuboid articulation are elevated, and a transverse calcaneal tunnel is drilled, so as to emerge on the lateral surface of the os calcis, in the region of the trochlear process. The guide suture previously passed through the tibia is now passed down along the inner aspect of the ankle, beneath the tendon of the tibialis posticus muscle and around the inferior surface of the os calcis. A small external counterincision is made, and from without inward a graft is passed back through a tunnel made in the os calcis. A small incision is now made over the fascia lata in the lower portion of the thigh. With the fascial stripper, a long strip of fascia is removed subcutaneously and is passed through the drill holes, exactly along the course of the guide sutures. The heel is strongly supinated, and the strands of the fascial graft are sutured to the bone and are then united to each other, if possible. The wound is closed in layers, and a plaster-of-paris boot is applied with the foot in the maximum of inversion. Immobilization is maintained for six weeks. On removal of the plaster, a well molded foot plate is prepared and the patient is allowed to bear weight in wedged shoes. He recommends the procedure particularly for adolescent patients, between the ages of 8 and 15, feeling that it has special merit since it is completely extra-articular and avoids the danger to the epiphysal growth zone.

382 Bergmann, E. Partial Giant Growth. Operative Reduction in Size of Foot, *Am J Surg* 55 548-549 (March) 1942.

383 Wagner, L. C. Bone Block for Paralytic and Spastic Equinus. Study of End Results for One Hundred Cases (1925-1940), *J Mt Sinai Hosp* 9 826-831 (Nov-Dec) 1942.

384 Milch, H. Reinforcement of Deltoid Ligament for Pronated Flat Foot. Inversion Fasciodesis of Os Calcis, *Surg, Gynec & Obst* 74 876-881 (April) 1942.

[ED NOTE—For feet that are normal in every way except for structural weakness it is sufficient, particularly in the adolescent, to bring the foot into varus and the anterior part of the foot in its normal relationship to the posterior part by means of the corrective shoe, and then follow through with normal exercises. In cases in which there is a true paralysis and such an operation would be of value, it is the opinion of one editor (E D W H) that the fascial structure would not be able to retain the position against the body force.]

Fitch and King³⁸⁵ describe an operation based on the principles of treatment described by Kidner and Lowman for correction of pes valgoplanus, which has failed to respond to conservative treatment. The procedure consists in a transposition of the insertion of the posterior tibial tendon and of the anterior tibial tendon. They also lengthen the tendo Achillis. They have found that this procedure is best suited to feet that have faulty foot posture with depressed longitudinal arches, rather than feet with completely flattened longitudinal arches.

[ED NOTE—The feet for which this operation is indicated, according to the authors' criteria, would respond to conservative treatment in most instances. Lengthening of the tendo Achillis tends to weaken the foot further and gradual stretching of the tendon is preferable. When there is an accessory scaphoid, removal of the accessory scaphoid with transplantation of the tendon after the manner of the authors is to be recommended.]

Kuhns³⁸⁶ states that weakness and other disturbances of the foot are found in more than 50 per cent of all small children, and many of them disappear spontaneously as skill in balance and walking develops. Five-tenths per cent of the feet show a persisting ligamentous relaxation. Unless properly treated this relaxation progresses and gives functional disturbance in adult life. There is a variation of the ligamentous relaxation in the feet of infants at birth. Severe changes all the way up to a typical pes calcaneovalgus congenitus have been described in the literature. From a study of feet of children during the past ten years with prolonged and discouraging attempts at correction we feel that this ligamentous relaxation with its many variations can best be called congenital flatfoot. At birth all show unusual relaxation. The cause is not clear, but available data suggest that it is inherited, behaving like a recessive trait. Treatment should be started in early childhood. The foot should be held while at rest and in weight bearing in inversion and with slight elevation of the longitudinal arch. In cases in which congenital flatfoot is not corrected by this treatment relief of symptoms can often be secured by proper shoes and by supports under the longitudinal arch and the inner side of the heel. For severe disability seen in adolescence or adult life, a surgical procedure which will hold the foot in a good weight-bearing position is usually required.

[ED NOTE—The emphasis on early recognition and early treatment of flatfoot is commendable.]

McFadyean³⁸⁷ stresses the fact that to obtain a correction of a hammer toe it is necessary to wait six weeks, until an arthrodesis occurs. To avoid a surgical operation he recommends the conservative method for taking pressure off the deformed toe by placing a dome-shaped metal raise on a shoe tree in the area where the shoe presses on the contracted toe. This raise on the shoe tree stretches the shoe sufficiently to allow space to prevent friction rub.

385 Fitch, R. R., and King, B. B. Operative Treatment of Relaxed Weak Feet. *J. Bone & Joint Surg.* **24**: 574-575 (July) 1942.

386 Kuhns, I. G. Congenital Flatfoot. *Arch. Pediat.* **58**: 755-763 (Dec.) 1941. Congenital Flatfoot, *J. A. M. A.* **120**: 329-333 (Oct. 3) 1942.

387 McFadyean, K. Prevention of Hammer-Toe Bursitis. *Lancet* **1**: 474 (April 18) 1942.

[ED NOTE—Conservative treatment by removal of the pressure is of value in those cases in which surgical intervention is contraindicated]

Von Pap³⁸⁸ describes a new apparatus for obtaining extension of the great toe following operations for hallux valgus and hallux rigidus. In cases in which the abnormality was bilateral he applied the apparatus on the one foot and a cast on the other and found that the feet treated with the cast showed greater stiffness than those to which the apparatus was applied. He suggests that traction be applied for the first three postoperative days. On the fourth and fifth days mobilization is begun. In this way he obtained better functional results.

In discussing perforating wounds of the foot, Bowen³⁸⁹ says. In dealing with nail puncture wounds incurred by the laborers in the construction of the United States Naval Air Station at Jacksonville, Fla., the following simple plan of treatment was used. The foot was soaked for fifteen to thirty minutes in hot water to which liniment of soft soap (tincture of green soap) or a quantity of saponated solution of cresol was added. (He does not believe the addition of these solutions affected the results.) The foot was dried carefully and an area 2 to 3 inches (5 to 7.5 cm) in diameter around the wound was painted with mercresin (ortho-hydroxyphenylmercuric chloride). The edges of the wound were grasped with splinter forceps, and the epidermis was cut away for several millimeters about the circumference of the wound. This exposed the foreign matter (usually sand, rarely particles of sock, leather, rust, rubber or concrete) which could then be easily removed with forceps or wiped away with a cotton applicator soaked in tincture of mercresin. The wound was not probed beyond $\frac{1}{4}$ inch (0.6 cm), and this was done under direct vision. A dry dressing was applied, and 1,500 U. S. P. units of tetanus antitoxin was given. If the wound was caused by a larger nail than 10 penny, the patient was instructed not to walk for one or two days, otherwise he returned to work at once. The patient was instructed to soak his feet in hot water for thirty minutes when he reached home and repeat at bedtime. Patients with severe wounds, caused by nails larger than 10 penny, were given crutches and told not to bear weight on the foot for one or two days. They reported to the hospital for further inspection on the day they returned to work. If there was any sign of increasing inflammation, rest and elevation and hot compresses were advised. Patients with minor wounds were instructed to return only if increased soreness was noted. No prophylactic treatment with a sulfonamide compound was used orally or locally. In this paper only patients who came for treatment on the day of injury are considered. Soaking the foot in hot water dilates the tissue capillaries, and this brings an exudation of lymph, the best germicidal agent in the body, into the affected area. Leukocytes are probably mobilized by the local elevation of temperature. There were no deaths in a series of 661 cases and no tetanus. Cavalry units were stationed at the sites of air stations during the first World War, and thus the nails were probably exposed to the tetanus bacillus. There was a total of four hundred days of disability in the 661 cases, six-tenths day of disability per case. Persons with disability due to tetanus antitoxin have not been considered in this series.

[ED NOTE—This is an excellent paper and in accordance with the findings of others who have dealt with large series of puncture wounds. A ten minute scrub with soap and water and a debridement of the skin area around the aperture, with a sterile dressing, have given similar results.]

388 von Pap, K. A New Apparatus to Promote Articulation After Operations on Great Toe, *Arch f orthop u Unfall-Chir* 41 116-118, 1941

389 Bowen, F. H. Report of Six Hundred and Sixty-One Nail Puncture Wounds of the Foot, *I. A. M. A* 119 413-414 (May 30) 1942

A survey of end results of several types of operation for hallux valgus was made, with analysis, by Nelson and Kaplan³⁹⁰. Their conclusions were as follows. For the group 20 to 40 years of age with mild involvement, the Stein and the McBride operation were effective. Exostectomy is also advisable although it is followed in this age group at times by recurrence of the exostoses especially on the dorsal surface. For persons in this age group with severe involvement cases the Kleinberg and the Lapidus operation are recommended, as they give good results even in the presence of arthritis, although the period of convalescence is long. The Keller operation can also be recommended as it proved satisfactory irrespective of age and severity in the few cases observed. For the group over 40 with mild deformity and absence of arthritis the Silver type of operation and exostectomy may be used with satisfactory results. The McBride and the Stein procedure are less satisfactory. The Kleinberg and the Lapidus operation may be used with success, especially from the patients' point of view, although convalescence is prolonged. With severe deformity and in the presence of arthritis exostectomy and the Silver operation are apparently not advisable because of recurrence of exostoses and pain. With the McBride and the Stein operation in several instances there were postoperative rigidity of the toe and recurrence of the deformity. The Lapidus and the Kleinberg operation are found satisfactory in spite of long convalescence. The Keller procedure, as observed in a few cases gives the impression of being the operation of choice for this age group in the presence of severe deformity and arthritis.

Johnstone³⁹¹ describes a case. He feels, after a diligent search through the literature, that this is the first published case of osteochondritis in the sesamoid of the second metatarsal. The clinical picture in this case corresponds to the generally accepted features of osteochondritis in sesamoids, and in the differential diagnosis there are only two conditions to be considered. These are developmental fissures and fractures. The former are usually bilateral, regular in outline, of uniform density and symptomless. The latter show irregular clefts with sharp margins, they are unilateral, and generally there is a history of injury. Restoration of bone structure, after passing through the various stages of osteochondritis, confirms the diagnosis.

Blumenfeld³⁹² discusses the supernumerary bones that occur around the ankle, the principal ones are the external tibial bone, the os trigonum, the os peroneale and the os vesalianum, and the less frequent ones in this region are the intermetatarsal bone, the accessory calcaneus, the uncinat bone and the intercuneiform bone. Illustrated reproductions of the roentgenograms of some of these are shown. In the author's opinion, in adolescence these supernumerary bones may be the seat of an epiphysitis causing pain. He recommends that painful supernumerary bones be extirpated, with local anesthesia.

[ED. NOTE.—It is not frequent that these sesamoid bones give rise to acute symptoms. Involvement of them is usually an incidental finding, and the important thing is to be able to differentiate it from fracture.]

Milch³⁹⁴ describes an operation for a calcaneus deformity. He reports a case in which the calcaneus deformity was due to an excessive lengthening of the achilles

390 Nelson, L. S., and Kaplan, E. B. Hallux Valgus. Survey of End Results of Various Operative Procedures for Correction of Hallux Valgus Performed at the Hospital During the Past Ten Years (1931-1940), *Bull. Hosp. Joint Dis.* 3: 17-25 (Jan.) 1942.

391 Johnstone, A. S. Case of Osteochondritis in Sesamoid of Second Metatarsal, *Brit. J. Radiol.* 15: 337-338 (Nov.) 1942.

392 Blumenfeld, I. Supernumerary Bones of Tarsus. *Semin. med.* 1: 852-858 (April 10) 1941.

393 Footnote omitted.

394 Milch, H. Elongation of Heel for Calcaneus Deformity. *J. Bone & Joint Surg.* 24: 870-872 (Oct.) 1942.

tendon in an attempt to correct an equinus deformity. Instead of simply shortening the achilles tendon, he turns down a posterior portion of the os calcis with the attachment of the achilles tendon and fills up the space with bone fragments. In this way the posterior projection of the os calcis and the distance of the achilles tendon from its center of rotation of the ankle joint was increased. The insertion of the achilles tendon was thus displaced downward. The author demonstrated that by increasing the lever arm to which the achilles tendon was attached he was able to restore the muscle balance.

[ED NOTE—It certainly is true that by increasing the lever arm one increases the power of the weakened muscle, but in this case it is also true that by extending the lever arm posteriorly one has also put more tension on the achilles tendon, which gives a relative shortening.]

Harding³⁹⁵ gives a description of a method for taking photographs of a foot with weight bearing, by means of a ground glass plate, mirrors and special lighting.

Krause³⁹⁶ tabulates the three stages of typical march foot, describing the roentgenologic changes. He believes that with technically perfect roentgenograms the first stage can be diagnosed more frequently.

Reckling³⁹⁷ points out the necessity for repeating the roentgenogram to prove the presence or absence of a fracture in case of a swollen foot when there is dorsal swelling over the metatarsal bone, since a march foot in its earliest stages may not show the fracture and after the roentgenogram is taken later it will show the fracture line.

Lapidus³⁹⁸ describes an operative procedure for correction of overlapping fifth toe which consists in running the distal stump of the extensor longus tendon, with its insertion intact, through an oblique spiral channel across the plantar surface of the toe and implanting it into the conjoined tendons of the abductor and short flexor muscles of the fifth toe, after dorsal and medial capsulotomy of the fifth metatarsophalangeal joint.

[ED NOTE—The operative procedure seems to be mechanically sound, because it not only corrects the main three components of the deformity but utilizes the muscle power of the abductor and the short flexor for active maintenance of the correction.]

Swanson's³⁹⁹ article covers a great deal of subject matter in that it includes the various types of fractures of the ankle, as well as fractures of the astragalus and fractures of the calcaneus. He stresses the rupture of the ligaments and their importance, displacement at the ankle joint due to a tear of the fibulotibial ligaments, and the dire consequences if such conditions are not recognized and adequately treated. He again stresses the relatively poor prognosis of fracture of the os calcis. He feels that the result is dependent on the involvement in the joint as well as the perfection of reduction. For crush fractures of the astragalus he advises an astragalectomy with posterior displacement of the foot.

A Barba Inclan⁴⁰⁰ reports the result of a study of 305 cases at the Policia Nacional, in which he studied sprains in the various parts of the body. The treat-

395 Harding, F. R. Photographing Plantar Surface of Feet with Weight Bearing, *J Biol Photographic A* **10** 113-115 (March) 1942.

396 Krause, G. R. March Fracture (Deutschlander's Disease, Pied Force), *Radiology* **38** 473-476 (April) 1942.

397 Reckling, F. Appearance of Roentgen Image of Fracture of Third Metatarsal Bone Only After Pressure on Foot, *Monatschr f Unfallh* **48** 8-12 (Jan) 1941.

398 Lapidus, P. W. Transplantation of Extensor Tendon for Correction of Overlapping Fifth Toe, *J Bone & Joint Surg* **24** 555-559 (July) 1942.

399 Swanson, J. C. Injuries of Ankle *Journal-Lancet* **62** 93-94 (March) 1942.

400 Barba Inclan, A. A Modern Concept of Joint Sprains, *Cir ortop y traumatol Habana* **9** 120-127 (July-Sept) 1941.

ment by means of the Leriche method was used, and in the author's opinion this gave the best results. However, he states that he used tutocaine instead of the usual procaine. In addition to the local anesthesia he used compressive strappings and physical therapy as adjuncts in the treatment.

Carothers,¹⁰¹ writing on sprains, points out that ordinary sprains in which there is a stretching of the external lateral ligament with a rupture of a few fibers but without complete rupture of the ligament will respond to strapping as well as to the treatment with local injection of procaine hydrochloride. He stresses the importance of a small number of cases in which the ligaments are torn, the tibio-fibular as well as the astragalofibular, and that the probability is that there has been a dislocation of the astragalus which has been reduced. After the reduction this can no longer be recognized by roentgen examination unless there is an injection of procaine hydrochloride which permits sufficient inversion of the foot to cause displacement which can be demonstrated roentgenologically. In these cases strapping or injection of procaine hydrochloride is inadequate, and great damage will be done if the patients are treated in this way.

CONDITIONS INVOLVING THE SHOULDER AND NECK

PREPARED BY J. G. KUHNS, M.D., BOSTON

Congenital Deformities—The so-called congenital torticollis is divided by Copland¹⁰² into three types: (1) primary congenital torticollis, which is the result of a congenital defect in the cervical portion of the spine or of a cervical rib; (2) secondary congenital torticollis, which is probably caused by a twisted position of the fetal head in utero, and (3) parturitional torticollis, which results from rupture or hematoma of the sternocleidomastoid muscle during delivery. The third type is the most common. Occasionally the scalenus muscle also is involved and may continue the deformity. The author advises section of the sternocleidomastoid. Occasionally the scalenus anterior must also be cut. A careful examination should be made at operation.

[ED. NOTE.—Section of the scalenus muscle is seldom necessary.]

In the course of examining recruits for the British Army, Grieve¹⁰³ found 2 young men with bilateral subluxation of the acromioclavicular joint. He concluded that these were examples of congenital subluxation since there was no history of injury and the men stated that the abnormal appearance of the shoulders had always been present. Roentgenograms confirmed the diagnosis of bilateral subluxation of the acromioclavicular joints. From a study of the pertinent literature the author concludes that this congenital deformity is rare.

Anatomy and Pathology—Gray¹⁰⁴ examined 1,239 human scapulas. Of 1,152 scapulas seen in the dissecting room 27 showed an absence of the muscular cristae on the anterior surface. One hundred and sixty-seven of 1,152 showed no sulcus for the circumflex scapular artery, and 28 had anomalous foramina. Costal facets were found in 64. The suprascapular notch was converted into a foramen in 73 of 1,151. Separate acromial bones were observed in 36 of 1,086 scapulas. Facets on the inferior surface of the acromion were found in 240 of 1,085 scapulas.

401 Carothers, R. G. Sprained Ankles, *Ann. Surg.* **115** 654-657 (April) 1942.

402 Copland, S. M. Scalenus Anticus Factor in Congenital Torticollis, *Surgery* **11** 624-631 (April) 1942.

403 Grieve, I. Bilateral Congenital Subluxation of Acromio-Clavicular Joint, *Lancet* **2** 424 (Oct. 10) 1942.

404 Gray, D. I. Variations in Human Scapulae, *Am. J. Phys. Anthropol.* **29** 57-72 (March) 1942.

Variations in the shape of the glenoid fossa were common. Among 1,151, 706 had convex vertebral borders. Three hundred and twenty-nine were straight, 114 were concave (scaphoid scapulas) and 2 were unclassifiable.

[ED NOTE—Too little attention is paid by clinicians to the minor anomalies about the shoulder as factors in the production of symptoms in this region.]

In a voluminous study of the scapula Hrdlička⁴⁰⁵ states that scapulas may be grouped into three main types: (1) triangular (wedge shaped), with the vertebral border straight, (2) concave, with the vertebral or both the vertebral and the axillary border concave and (3) convex, with the vertebral border convex. He concludes that the shape of the scapula is partly of functional causation. Weakening of the musculature about the clavicle may cause concavity. About 10 per cent of the scapulas examined were concave. Usually both sides of the skeleton will show the same type of clavicle. The triangular scapula with a straight vertebral border is far more common in adults than in children. Concave scapulas are more common in children. The juvenile scapula is far from being finished in its form. The superior border of the scapula is its most variable part and changes shape throughout the growing period.

Makowski⁴⁰⁶ attempts to trace in sequence the development of calcific deposits in the supraspinatus tendon. There is first inflammation of the tendon, with some necrosis which is followed by deposition of calcium. The commonest cause of inflammation is pinching of the supraspinatus tendon. Subdeltoid bursitis follows the changes in the tendon. The morbid anatomy in a 36 year old epileptic woman who had had frequent anterior dislocation of the right shoulder was reported by Eyre-Brook⁴⁰⁷. The patient died while a Nicola operation was being performed. At autopsy a tear of the anterior ligament from the attachment of the biceps muscle to the bottom of the glenoid cavity was found, as has been described by Bankart. There was a large notchlike depression on the posterior surface of the humeral head. This was caused by erosion of cartilage and absorption of bone from recurrent trauma.

Odgers and Hark⁴⁰⁸ report observations on habitual dislocation of the shoulder. They found 6 tears in 40 shoulders examined in the dissecting room. They interpreted these to be degenerative changes or incomplete repair. Twelve patients with habitual dislocation were seen. No recurrences were seen following the Bankart operation.

From roentgenologic studies, Sachs and Hill⁴⁰⁹ conclude that inferoanterior dislocations of the humeral head are caused by the application of force through the longitudinal axis of the humerus with the shoulder abducted and internally rotated. The degree of internal rotation determines whether the glenoid lip will impinge on the posterolateral aspect of the humeral head with a resulting compression defect of the head. If the arm is in slight internal rotation, the glenoid lip will impinge on the greater tuberosity and produce an avulsion fracture of the

405 Hrdlička, A. Scapula. Visual Observations, *Am J Phys Anthropol* **29** 73-94 (March) 1942.

406 Makowski, S. J. Calcific Deposits in Supraspinatus Tendon, *M Times, New York* **70** 19-22 (Jan.) 1942.

407 Eyre-Brook, A. L. Morbid Anatomy of Case of Recurrent Dislocation of Shoulder, *Brit J Surg* **30** 32-37 (July) 1942.

408 Odgers, S. L., and Hark, F. W. Habitual Dislocation of Shoulder Joint, *Surg Gynec. & Obst* **75** 229-234 (Aug.) 1942.

409 Sachs, M. D., and Hill, H. A. Complications of Infero-Anterior (Axillary) Dislocation of Shoulder Joint as Demonstrated by Roentgenograms, *Surg, Gynec. & Obst* **75** 639-646 (Nov.) 1942.

tuberosity. Fractures of the glenoid lip are produced when the shoulder is in internal rotation. When pain persists for a long period after injury roentgenograms of the bicipital groove will sometimes show lesions in this area.

Jones⁴¹⁰ reports 2 instances in which it was necessary to remove the humeral head for comminution associated with dislocation. After the removal of the fragments the proximal end of the humerus was rounded and the capsular subscapularis, supraspinatus, infraspinatus and teres minor muscles were reattached to the humerus. Almost normal function resulted. The four muscles act as a unit in stabilizing the shoulder in abduction. Movement of the shoulder joint demands contact of the head of the humerus and the glenoid cavity. The author believes that there is a great deal of difference between the shoulder joint in relaxed motion and when heavy work is being done. The fixation produced by the capsular muscles produces stability of the shoulder joint in motion.

Symptomatology—Hoobler⁴¹¹ reports the case history of a patient with thrombosis of the subclavian artery associated with cervical rib. The thrombosis was followed by a right hemiplegia, which disappeared in sixteen days. Five similar cases reported in the literature are reviewed. The thrombosis was believed to have resulted from prolonged arterial spasm caused by the cervical rib. Cerebral embolism from such thrombosis can occur only on the right, where the common carotid and subclavian arteries come off from the innominate artery.

Pain in the arm, brachialgia, should be considered not as a disease entity but as the result of irritation or pressure on nerves in the cervical region.⁴¹² The scalenus anticus muscle is not primarily responsible. Compression of the nerve roots at the intervertebral foramina is frequently the cause.

Torticollis as a result of motor disturbances of the eye is not often seen by the orthopedic surgeon. Guy⁴¹³ discusses the diagnosis of such lesions. If no vertical oculomotor error is found the eyes can be ruled out as a cause of torticollis unless ptosis of a lid is present. Ocular torticollis is associated with an attempt at single binocular vision and is not found in the newborn. Ocular torticollis often follows forceps delivery. No facial asymmetry results from this deformity which is commoner than is realized.

Ilfeld and Holder⁴¹⁴ report the case history of a patient in whom weakness of the anterior serratus muscle was due to carrying a knapsack. The condition probably resulted from stretching the long thoracic nerve in swinging the pack onto his back. Treatment consisted of support with a sling, heat and massage. Complete recovery occurred in four weeks.

Howard⁴¹⁵ states that injuries about the shoulder girdle comprise 11 per cent of industrial injuries and 12 per cent of industrial disabilities. For acromioclavicular dislocation he describes his method of maintaining continuous elastic

410 Jones, L. Shoulder Joint. Observations on Anatomy and Physiology with Analysis of Reconstruction Operation Following Extensive Injury, *Surg, Gynec & Obst* **75** 433-444 (Oct.) 1942.

411 Hoobler, S. W. Syndrome of Cervical Rib with Subclavian Arterial Thrombosis and Hemiplegia Due to Cerebral Embolism. Report of Case, *New England J. Med* **226** 942-944 (June 11) 1942.

412 Morse, F. W. Cervical Ribs and Scalenus. *Nov. Scotia M. Bull* **21** 318-324 (Nov.) 1942.

413 Guy, L. P. Ocular Torticollis. Differential Diagnosis, *Arch. Ophth* **28** 17-26 (July) 1942.

414 Ilfeld, F. W., and Holder, H. G. Winged Scapula. Case Occurring in Soldier from Knapsack. *J. A. M. A* **120** 448-449 (Oct. 10) 1942.

415 Howard, N. I. Symposium on Industrial Surgery. Diagnosis and Treatment of Certain Injuries of the Shoulder Girdle. *S. Clin. North America* **22** 1049-1073 (Aug.) 1942.

traction on the outer end of the clavicle for five weeks. All such dislocations heal if treatment is continued long enough. He advises early active exercise for injuries about the shoulder.

Bennett⁴¹⁶ believes that periarthritis most fully describes the usual painful contracted shoulder. The cause is obscure, but repeated trauma plays an important part. Treatment is first designed to secure relaxation of muscular spasm. This is accomplished by fixation of the shoulder in a comfortable position with sandbags and pillows and by the application of heat, preferably hot compresses. Massage is given cautiously and is followed by passive and active motion. If there is no increased range of motion after a forty-eight hour period manipulation with the patient under anesthesia is indicated.

Treatment—Travell, Rinzler and Herman⁴¹⁷ report the results of intramuscular infiltration with 1 per cent solution of procaine hydrochloride for the relief of pain in the shoulder. The 58 patients studied had a tender point in the muscles about the back and shoulder girdle, pain on motion of the arm and limitation of active movement. Full restoration of movement and remission of pain followed this treatment in 62 per cent of the cases. The writers suggested that impulses arose in one or more foci in the muscle and reflexly led to the symptom, restriction of motion was primarily a reaction to pain.

[ED NOTE—While intramuscular injections of procaine hydrochloride will at times lead to abatement of pain, we feel that treatment of the patient should be based on as exact a diagnosis of the disability as can be made.]

In the treatment of 32 patients with painful shoulders Kelly⁴¹⁸ gave 16 of them injections of 20 cc of a 1:200 solution of procaine hydrochloride into or just beneath the upper fibers of the trapezius muscle with complete relief of symptoms. He believed that in these patients there was a trophic nervous reflex which caused the symptoms. This type of lesion should be differentiated from brachial neuritis.

Chapman⁴¹⁹ used roentgenotherapy for 54 painful shoulders, giving 250 r twice a week for four or five treatments. More rapid relief was observed in patients who came for treatment early in the course of the disease. Seventy-seven per cent of the shoulders were cured.

Anesthesia of the cervical portion of the sympathetic nervous system will relieve the pain in the scalenus anticus syndrome. Judovich and Bates⁴²⁰ advocate injection of procaine hydrochloride into the scalenus anterior muscle. Following this Horner's syndrome will be observed occasionally, but only temporarily. Operation on the scalenus muscle should be deferred until a successful muscular infiltration has been obtained without sympathetic effect. If symptoms are not relieved by such infiltration, operation is indicated.

Reichert⁴²¹ advises relaxation of the scalenus muscle by special positions in bed and at work to relieve the accompanying brachial neuritis. The shoulder is elevated with a sling. Work that aggravates symptoms is avoided. In bed the patient lies

416 Bennett, R. L. Painful Contracted Shoulder, *Brit J Phys Med* 5: 69-72 (April) 1942.

417 Travell, J., Rinzler, S., and Herman, M. Pain and Disability of Shoulder and Arm. Treatment by Intramuscular Infiltration with Procaine Hydrochloride, *J A M A* 120: 417-422 (Oct 10) 1942.

418 Kelly, M. New Light on Painful Shoulder, *M J Australia* 1: 488-493 (April 25) 1942.

419 Chapman, J. F. Subacromial Bursitis and Supraspinatus Tendinitis. Its Roentgen Treatment, *California & West Med* 56: 248-251 (April) 1942.

420 Judovich, B. D., and Bates, W. Scalenus Anticus Syndrome, *I Internat Coll Surgeons* 5: 26-32 (Jan-Feb) 1942.

421 Reichert, F. L. Compression of Brachial Plexus. Scalenus Anticus Syndrome. *J A M A* 118: 294-296 (Jan 24) 1942.

with the head in forward flexion. Two to four weeks of such treatment is usually required for relief of symptoms. He states that 60 of 74 patients were relieved by this treatment and 14 required scalenotomy.

Hansson⁴²² states that 85 per cent of patients with the scalenus anticus syndrome can successfully be treated by conservative measures. He advises recumbency in bed with the arm suspended over the head. When the patient becomes ambulatory a figure of eight bandage or an aeroplane splint for the arm is applied. Exercises also are given to elevate and abduct the scapula. Heat is applied to the shoulder and an attempt is made to improve posture.

[ED NOTE—Forward flexion of the neck will lead to only temporary relief in the presence of contracture of the scalenus anterior muscle. If there is an associated cervical arthritis the symptoms will be made worse. Conservative treatment to be effective and lasting must secure an improved position of use and carriage of the entire shoulder girdle and neck, with the chest held high and the shoulder up and with very little lordosis in the cervical portion of the spine.]

In the treatment of injuries to the acromioclavicular joint, Thorndike and Quigley⁴²³ counsel conservatism. They have observed 173 such injuries, most of them partial tears of the ligaments. Such tears are demonstrated by increased mobility in this region. They advocate strapping the joint with adhesive tape over a felt pad. This dressing is changed every two days. Diathermy also is given. In most cases symptoms were relieved in eight days.

Among the operative methods of repair of acromioclavicular dislocation Phemister⁴²⁴ advises a curved incision over the acromioclavicular joint. A wire is placed through the acromion and the distal 1 inch (2.54 cm) of the clavicle. The wire protrudes laterally and is later removed. Two case histories are reported. Tyler⁴²⁵ employs procaine hydrochloride anesthesia and passes a screw obliquely through the clavicle into the acromion. A satisfactory end result was observed after two months. Vargas⁴²⁶ states that in incomplete acromioclavicular dislocation nonoperative procedures usually are satisfactory but that they are not satisfactory for complete dislocation. A saber incision is made over the anteromedial aspect of the shoulder. The deltoid muscle is separated anteriorly in line with its fibers and the coracoid process is exposed. The short head of the biceps muscle is split longitudinally for 6 cm. A hole is drilled through the clavicle. The free portion of the biceps muscle is then threaded through the hole and sutured to itself. The shoulder is immobilized for twenty days.

Bost and Inman⁴²⁷ have found that the essential lesion in anterior dislocation of the shoulder is a tear of the glenoid labrum as described by Bankart. This is not seen in the usual operative approaches for repair. They report the pathologic changes observed in 10 patients who were operated on by Bankart's technique. In addition to the tear in the glenoid labrum, a defect in the posterolateral aspect of

422 Hansson, K. G. Scalenus Anticus Syndrome, *S. Clin. North America* **22** 611-620 (April) 1942.

423 Thorndike, A., Jr., and Quigley, T. B. Injuries to Acromio-Clavicular Joint. Plea for Conservative Treatment, *Am. J. Surg.* **55** 250-261 (Feb.) 1942.

424 Phemister, D. B. Treatment of Dislocation of Acromioclavicular Joint by Open Reduction and Threaded Wire Fixation, *J. Bone & Joint Surg.* **24** 166-168 (Jan.) 1942.

425 Tyler, G. T., Jr. Acromioclavicular Dislocation Fixed by Vitallium Screw Through Joint, *Am. J. Surg.* **58** 245 (Nov.) 1942.

426 Vargas, L. Repair of Complete Acromioclavicular Dislocation, Utilizing Short Head of Biceps, *J. Bone & Joint Surg.* **24** 772-773 (Oct.) 1942.

427 Bost, F. C., and Inman, V. T. Pathological Changes in Recurrent Dislocation of the Shoulder. Report of Bankart's Operative Procedure, *J. Bone & Joint Surg.* **24** 595-613 (July) 1942.

the humeral head and a fracture or erosion of the glenoid rim were observed. The stages of the operative procedure are: 1. A long incision is made, with separation of the deltoid and the pectoralis major muscle and partial separation of the pectoralis major from the humerus. 2. The tip of the coracoid is detached and turned downward and medially. 3. The humerus is rotated outward, and the subscapularis tendon is divided near its insertion. 4. The tear in the glenoid labrum is seen. 5. The glenoid rim is raised with a chisel, and the anterior capsule is sutured to the bone. 6. The arm is bandaged to the side for six weeks. Eight patients have been observed for a sufficiently long time to permit evaluation of the treatment. Seven have had no recurrence of the dislocation. One, who had epilepsy, had a recurrence of the dislocation three weeks after operation.

Nicola⁴²⁸ advises operation on young, vigorous persons at the time of the first dislocation of the shoulder. The capsule should be resutured, and the long head of the biceps muscle should be passed through the humeral head at least $\frac{1}{2}$ inch (1.3 cm) from the edge of the articular cartilage. In recurrent dislocations the capsule should be explored to determine the location of the tear. The shoulder should then be reenforced with the long head of the biceps muscle and the strip of capsule which lies above it.

Raney and Miller⁴²⁹ report the end results for 26 patients suffering from recurrent dislocation of the shoulder who were treated by the Nicola procedure. Sixty-five per cent were cured. Nine patients were less disabled than before but had recurrence of the dislocation.

Modifications of the Nicola operation are described. Wahl⁴³⁰ attaches the distal end of the biceps tendon to the periosteum just below the greater tuberosity. Suture of the distal portion is performed with the arm in 45 degrees of flexion. The proximal end is brought through a hole in the greater tuberosity and attached to the periosteum with the shoulder in 45 degree abduction. The arm is held in this position with a spica for three weeks. This is followed by physical therapy. Thirty-one patients have been operated on by this method with only 1 recurrence. Glassman⁴³¹ avoids drilling through the articular surface of the humeral head. An incision is made downward from the coracoid splitting the deltoid fibers. With the shoulder in 45 degree abduction and the elbow midway between pronation and supination, the long head of the biceps muscle is split lengthwise. Flexing the elbow brings more of the intracapsular portion of the tendon into view. The split portion of the tendon is pushed up through its canal and is then threaded through a hole in the lesser tuberosity and fastened there. No results of this procedure are reported.

Milgram⁴³² reports the history of an 8 year old girl who crawled but did not walk until the age of 3 years. There was marked forward displacement of the shoulders, so that anteriorly they could be brought almost together. A cuneiform osteotomy was performed in the outer third of each clavicle, after which a plaster shoulder dressing was worn for six weeks. A greatly improved appearance resulted.

428 Nicola, T. Anterior Dislocation of Shoulder. Role of Articular Capsule, *J. Bone & Joint Surg.* **24** 614-616 (July) 1942.

429 Raney, R. B. and Miller, O. L. Nicola Operation for Recurrent Dislocation of Shoulder. Review of Twenty-Six Cases, *South M. J.* **35** 529-532 (May) 1942.

430 Wahl, S. Operative Treatment for Recurrent Dislocation of Shoulder, *Ann. Surg.* **115** 441-444 (March) 1942.

431 Glassman, J. A. Extra Articular Operation for Recurrent Dislocation of the Shoulder. *Joint Surg., Gynec. & Obst.* **74** 755-759 (March) 1942.

432 Milgram, I. E. Congenital Forward Shoulders (Quadrupedal Type). Treatment by Clavicular Osteotomy. *Bull. Hosp. Joint Dis.* **3** 93-96 (July) 1942.

NERVOUS REGULATION OF CLOTTING MECHANISM

GÉZA DE TAKATS, M.D.

CHICAGO

In a previous communication¹ I described a simple clinical test of the clotting mechanism which consists of the injection of 10 mg (1 cc) of purified heparin intravenously and the determination of capillary coagulation times before and ten, twenty, thirty and forty minutes after the injection. It was found that the reaction to heparin is rather constant in the normal person but that it significantly changes to a diminished response in the first few days after major operations, in Buerger's disease and following all types of thromboses. Under the influence of sulfur compounds the hyporeactivity to heparin could be temporarily corrected.²

In this report I wish to submit some observations regarding the effect of autonomic nervous innervation on the heparin curve. Cannon and his co-workers³ have convincingly shown that epinephrine injected in small amounts intravenously or in larger doses subcutaneously will shorten the coagulation time from one half to one third of the original level. Stimulation of the splanchnic nerves resulted immediately or after a brief delay in the shortening of the coagulation time, which could last as long as thirty minutes. The stimulation usually produced less marked effects when it was repeated when the adrenal gland was removed on the side of splanchnic stimulation, the coagulation time remained unchanged, whereas on the opposite side the stimulation was still effective. The faster clotting time could therefore be attributed to discharge from the adrenal glands under stimulation of the nerves of the liver and

intestines did not alter the coagulation time, so that adrenal discharge was necessary to act on the liver or intestines. The effect of the discharge was abolished when the liver and other abdominal viscera were excluded.

When afferent nerves (sciatic or celiac) were stimulated, or if major operations were done with the subject under light anesthesia, the coagulation time became markedly shorter. Emotional excitement of the animal resulted in rapid coagulation times (as short as one-half minute), which could be restored to normal by bilateral splanchnic section. Cannon regarded this phenomenon as one more evidence of the adaptive reactions which serve the organism in case of injury.

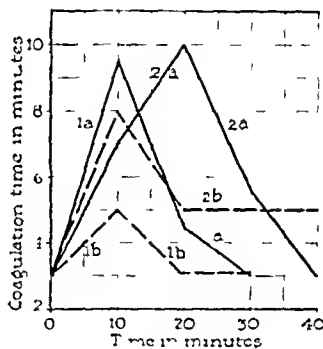


Fig 1—Effect of epinephrine on the heparin curve. Note that in both patients, who happened to be hyper-tensive hyperreactors,¹ the curves were lower after the intravenous injection of 0.001 mg of the drug. The continuous line is the curve before administration of epinephrine, the broken line, after.

Vagal stimulation, on the other hand seemed to prolong the coagulation time according to the observations of Plattner and Kodera⁴ and Zunz and La Barre.⁵ A study of their data however is not too impressive, since the differences were not great before and after stimulation. Instead of using a single determination of the clotting

From the Department of Surgery, University of Illinois, and the St. Luke's Hospital. This study was aided by a grant received from Hoffmann-La Roche, Nutley, N. J.

1. de Takats, G. The Response to Heparin. A Study of the Clotting Mechanism, *Surg., Gynec. & Obst.* 31, 1943.

2. de Takats, G. The Effect of Sulfur Compounds on Blood-Clotting, *Surgery* 14:661, 1943.

3. Cannon, W. B., and Gray, H. Factors Affecting Coagulation Time of the Blood. II. Hastening or Retarding of Coagulation by Adrenalin Injections. *Am. J. Physiol.* 34:232, 1914. Cannon, W. B., and Mendenhall, W. L. III. Hastening of Coagulation by Stimulating the Splanchnic Nerves. *ibid.* 34:245, 1914. IV. Hastening of Coagulation in Pain and Emotional Excitement. *ibid.* 34:251, 1914.

4. Plattner, F., and Kodera, A. Der Einfluss der Vagusreizung auf die Gerinnungszeit des Blutes. *Pflüger Arch. f. d. ges. Physiol.* 219:564, 1928.

5. Zunz, E., and La Barre, J. Action de la celiac et de ses dérivés dans la coagulation du sang. *Compt. rend. Soc. de biol.* 90:121, 1924. Action de la celiac et de l'acetylcholine sur la transformation du prothrombène en sérozyme. *ibid.* 90:655, 1924.

time to study the extent of these neurogenic influences, the heparin curve, a tolerance test was utilized by my associates and me since it was much more sensitive to a change in clotting factors. In addition, these studies revealed another heretofore unrecognized phenomenon, namely, that the human response to heparin is biphasic.

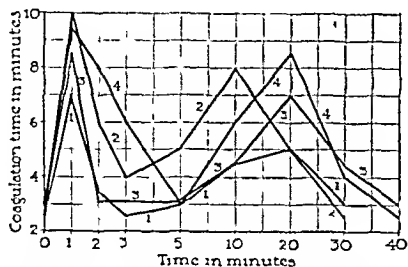


Fig 2—The biphasic reaction to heparin. The first phase is over in five minutes and is therefore completely missed in the usual test for heparin tolerance. The second phase lasts from thirty to forty minutes. The shape and duration of these two curves suggest that their mechanism is not identical.

OBSERVATIONS

The Effect of Epinephrine on the Heparin Curve—In two hypertensive patients who received 0.001 mg of epinephrine intravenously, it was found that this drug markedly inhibited the reaction to heparin (fig 1). For the first patient the coagulation time rose only to five minutes, instead of eight minutes, and the curve promptly returned to normal at twenty minutes, whereas for the control it took another ten minutes for the clotting time to return to normal. For the second patient the peak of the heparin

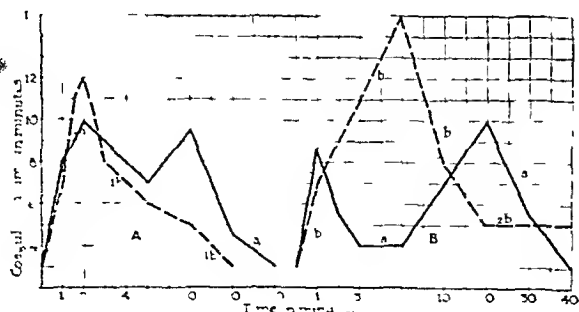


Fig 3—Note that epinephrine has exaggerated the first and depressed the second phase. Epinephrine may have mobilized an antiheparin factor (prothrombin?). 1 shows the curves for Hilda F, who had hypertension, B, for Belle S, with the same condition. The continuous line is the curve before administration of epinephrine, the broken line, after.

curve was reached only at twenty minutes, after epinephrine was given the curve had already markedly dropped and showed a clotting time of five instead of ten minutes. These observations could be repeatedly duplicated.

The analysis of these curves, however, led to the surprising discovery that the heparin curve really represents a biphasic reaction, of which usually only the second phase has been measured. Thus if the coagulation time is determined several times during the first five minutes a rise

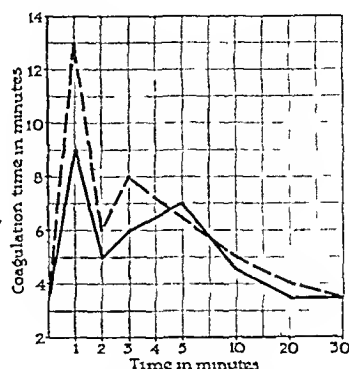


Fig 4—Mecholyl markedly exaggerates the first and slightly exaggerates the second phase of the heparin curve. Mecholyl is known to mobilize epinephrine. The continuous line is the curve before administration of 10 mg of mecholyl, the broken line, after.

and fall of the coagulation time can be observed which escapes one's notice if the determinations are made at the customary intervals of ten minutes (fig 2). Uniformly the curves are seen to rise and fall. These curves reveal that the inhibiting action of epinephrine is exerted on the second phase, since the first phase, especially in the case of Belle S may be markedly exaggerated (fig 3).

The Effect of Parasympathetic Stimulants on the Heparin Curve—Interestingly enough, the subcutaneous injection of mecholyl markedly

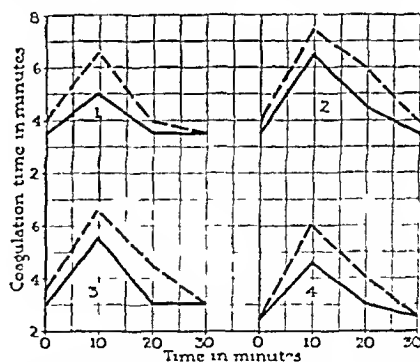


Fig 5—The effect on the heparin curve of prostigmine 1:2,000 given subcutaneously. The continuous line indicates tolerance to heparin before administration of 1 cc of prostigmine in a dilution of 1 to 2,000, the broken line, thirty minutes after.

exaggerates the first phase of the heparin curve and only slightly potentiates the second (fig 4). One cubic centimeter of prostigmine 1:2,000 given subcutaneously, usually raises the heparin curve (fig 5). This drug has been given in a series of cases in the gynecologic service of Dr

H O Jones at St Luke's Hospital every four hours for forty hours. As shown in my first communication,¹ the heparin curves usually become flat on the first two to four days after operation and this is the time when the danger of initial thrombosis is the greatest (fig 6). The prostigmine medication, however, prevents the flattening of the curve on the first few days, and even the lowest curves shown (figs 7 and

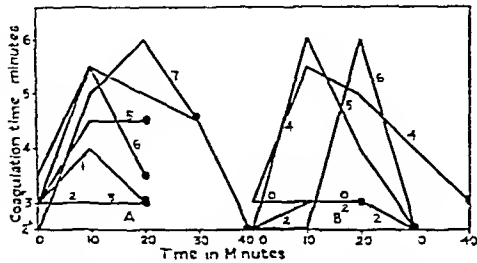


Fig 6—Postoperative resistance to heparin. Note that in Helen W there is complete lack of response to heparin on the second and third postoperative days. In Marie H the response is absent on the day of operation and extremely poor on the second postoperative day (from de Takats, G. Heparin Tolerance, Surg, Gynec & Obst 77 31, 1943). A shows the curves for Helen W with a ruptured appendix and diffuse peritonitis, B, those for Marie H with congenital hypoplastic kidney and hypertension who had undergone nephrectomy.

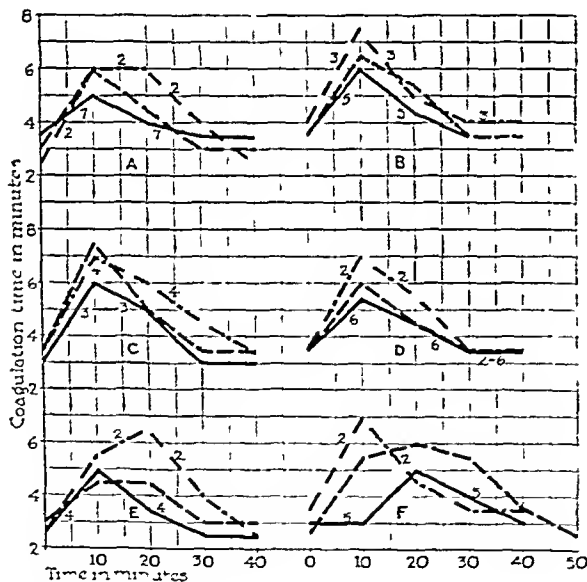


Fig 7—Daily heparin curves following subtotal hysterectomies during and after medication with prostigmine. Note that the usual flattening of the postoperative curves is absent and even the flattest curves are within normal limits. The curves on the second day, which are usually the flattest, are quite high because of the medication. The patients received 1 cc. of prostigmine, 1:2,000, every four hours for forty hours. A shows the curves for Mary McH, aged 34, B, for Mary M, aged 68, C, for Marie Th, aged 28 (she had a sensitization reaction on the fourth day), D, for Margaret O'C, aged 80, E, for Ruth B, aged 34, and F, for Gertrude S, aged 43. The dash line is the preoperative curve, the dash and dot line, the highest curve, and the continuous line, the lowest curve.

8) are within the normal range. On the second day, when one is accustomed to see a flat curve the curves are higher than they were preoperatively, owing to the medication with prostigmine.

RESULTS

There can be no doubt that the adrenergic and cholinergic components of the autonomic nervous system exert an effect on the clotting mechanism. The discharge of the adrenals, as Cannon³ has shown, shortens coagulation time and he suggested that epinephrine acts by causing the discharge of something from the liver and intestines which hastens coagulation.

The Viennese school of physiology first brought to notice a factor controlling the venous outflow from the liver by a sluice mechanism.⁶ The pharmacologic response of these sphincters situated near the caval opening of the hepatic veins has been extensively studied.⁷ Histamine

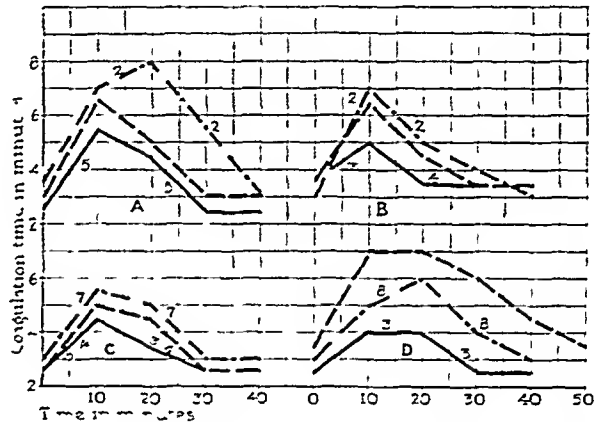


Fig 8—Four additional series of curves on hysterectomized patients during and following medication with prostigmine. Note that in the case of Lena T and Augustine V the curves were flat in spite of medication. In the first of these patients a postoperative thrombosis developed, manifest on the fourteenth day. The patients received 1 cc. of prostigmine, 1:2,000, every four hours for forty hours. A shows the curves for Victoria Th, aged 47, B, for Eunice S, aged 40, C, for Lena T, aged 65, and D, for Augustine V, aged 49. The dash line indicates the preoperative curve, the dash and dot line, the highest curve, and the continuous line, the lowest curve.

closes, epinephrine opens, these sphincters, there is, however, considerable variation in different species of animals and according to the doses employed. Since plasma prothrombin is manu-

6 Mautner, H, in Pick, E P. Ueber die durch Schockgifte erzeugten Zirkulationsstörungen, München med Wchnschr 62 1141, 1915.

7 Bauer, W, Dale, H H, Poulsson, L T, and Richards, D W. The Control of Circulation Through the Liver, J Physiol 74 343, 1932. Tamter, M L, and Dock, W. Further Observations on the Circulatory Actions of Digitalis and Strophantun with Special Reference to the Liver and Comparisons with Histamine and Epinephrine, J Clin. Investigation 8 485, 1930.

factured—at least to a great extent—in the liver, it seems possible that sympathetic nervous stimuli may discharge prothrombin from the liver. This view is supported by the observation of an increase in the level of prothrombin after epinephrine or neosynephrin. Conversely the cholinergic parasympathetic drugs, such as mechoyl and prostigmine, close the hepatic veins and prevent a steady supply of prothrombin flowing from the liver. The behavior of the heparin curve after adrenergic and cholinergic stimuli would then reflect changes in prothrombin levels.

There are other possible mechanisms to be considered. Heparin is manufactured in the mast cells of Ehrlich, from which it is discharged into the vascular system. The mast cells have been shown to empty in peptone shock.⁸ In peptone shock the blood is incoagulable and contains an excess of heparin. It is conceivable that drugs constricting or dilating blood vessels may empty or retain the heparin content of the mast cells. Thus a vasoconstrictor closes, a dilator opens, the small communications of the mast cells with the vascular tree. This problem can be attacked only by adequate histologic technique, and such studies are now under way.

Finally, one must regard these autonomic stimuli as possibly affecting the quantity of thromboplastic substances circulating in the blood. There is, however, no quantitative evidence of such an effect.

Whatever the mechanism, or mechanisms, are which bring about the changes in the clotting of the blood following autonomic stimuli, it is certain that they operate in the human being subjected to such stimuli. In certain patients such states of fear and anxiety develop before operations that their blood pressure and blood sugar and temperature rise, in others the stress of an argument or a tiring conference develops

8 Jorpes E, Holmgren M, and Wilander O. Ueber das Vorkommen von Heparin in den Gefasswanden und in den Augen. *Ztschr f mikr-anat Forsch* 42: 279, 1937.

thrombosis, in railroad engineers alighting from a strenuous transcontinental trip a cardiovascular accident sometimes occurs. There seems to be a lag between the time of the actual nervous stress and the actual clotting phenomenon.⁹

The clotting time shortens after hemorrhage, this reaction is an expression of a sympathetic excitation of the adrenals, accompanied by increased heart rate, panting and marked sweating.¹⁰

These stimuli are of diencephalic origin, diencephalic depressants, such as the barbiturates, are capable of relieving anxiety before operation, their preoperative and postoperative use is indicated. Postigmine in our experience has improved the clotting tendency of the postoperative state and is useful to combat postoperative atony of the intestines and bladder. Patient's fear of thrombosis may actually contribute to its occurrence.

In another publication, with Petersen¹¹ the effect of weather on thrombosis and embolism was discussed. It is more than likely that climatic conditions affect man through the autonomic nervous system.

SUMMARY

The clotting mechanism of patients, as tested by their response to heparin, is under neurogenic influence. Adrenergic stimuli increase, cholinergic stimuli decrease, the tendency to thrombosis. Fear, apprehension, nervous strain and hemorrhage increase the tendency to clotting, prostigmine, a drug frequently used as postoperative medication, by its cholinergic action lessens the postoperative tendency to thrombosis.

122 South Michigan Avenue

9 Gilbert, N C. Personal communication to the author.

10 Freeman, N E. Hemorrhage in Relation to Shock. Experimental Effect of Intravenous Injection of Saline, Gum Acacia and Blood on the Rate of Adrenal Secretion Resulting from Hemorrhage, *Ann Surg* 101: 484, 1935.

11 de Takats, G, and Petersen, W S. The Meteorologic Factor in Pulmonary Embolism, *Surgery* 7: 819, 1940.

SIGNIFICANCE OF SUPRACLAVICULAR SIGNAL NODE IN PATIENTS WITH ABDOMINAL AND THORACIC CANCER

A STUDY OF ONE HUNDRED AND TWENTY-TWO CASES

ENRIQUE P VIACAVA, M.D., AND GEORGE T PACK, M.D.
NEW YORK

The significance of metastasis to lymph nodes in the supraclavicular space secondary to cancer originating in the abdominal and thoracic viscera has long been of interest to surgeons and pathologists. Virchow¹ in 1848 first recognized the necessity for a careful examination of the supraclavicular fossa in patients with abdominal tumors. In 1889, Troisier² published a study of 27 primary abdominal tumors, the majority

in the stomach, which had metastasized to supraclavicular nodes. The eponyms of Virchow's or Troisier's node have been popularly used to this day.

Invasion of the supraclavicular nodes by cancer originating within the abdominal or thoracic cavity may become apparent during the course of development of the primary tumor, or the signal node may appear as a terminal manifestation of generalized cancer, or in some remarkable instances the enlarged supraclavicular nodes may constitute the only clinical evidence of cancer, the primary site of which remains to be found.

Unfortunately the discovery of these metastatic lesions connotes a poor prognosis with practically no possibility of curative treatment. In only a few exceptional cases has any control of the cancer been obtained for any appreciable length of time. Many attempts have been made during the last two decades to treat the metastatic cancer in the signal nodes by radiation therapy. But the nature of the extension and the origin of the cancer afford sufficient explanation for the failure of efforts at palliative irradiation and the contraindication for surgical intervention.

In the Memorial Hospital abundant clinical material is available for a study of metastasis to supraclavicular nodes; these data are supplemented by necropsy records. A thorough analysis was made of these visceral cancers, at which time it was observed that not all of them exhibited the same tendency to spread through the lymphatic system, resulting in supraclavicular metastases. Many variations have been found with relation to the primary site of the tumor and the nature and degree of malignancy of the cancer, thus making it difficult to compile the results of the different investigations and to obtain definite answers to these problems. Of 4,365 patients with abdominal and thoracic tumors who were treated in the last two decades in the Memorial Hospital, only 122 presented supraclavicular metastases, that is 2.8 per cent.

The cases employed in this study had the diagnosis verified in each instance by pathologic examination either by study of an excised node or by aspiration biopsy.

From the Gastric Service of the Memorial Hospital for Cancer and Allied Diseases

1 Virchow (*Zur Diagnose der Krebse im Unterleibe*, Med Reform, 1848, p 248) suggested the importance of examining the region of the jugular veins in patients with obscure abdominal disease. He stated that "because of the constancy of the connection between the abdominal organs and the lymph nodes in the neck, one sees in no other place in the body, the peculiar, coincident disease of the last with the cancerous condition of the first." The discovery and proper interpretation of the enlarged supraclavicular node were heralded as important for determining the nature of the abdominal disease. The presence of this lymph node may be the first sign of evidence of an abdominal tumor, but the absence of such a node has no prognostic importance whatsoever.

2 Troisier (*L'adenopathie sus-claviculaire dans les cancers de l'abdomen*, Arch gen de med 1 129-138 and 297-309, 1889) drew conclusions from his study which are equally valid today. Although cancer propagates usually from node to node, distant lymphatic metastases, e.g. from perigastric nodes to supraclavicular nodes, may occur without involvement of intermediate lymph nodes. In this dissemination, the cancer cells may pass along the thoracic duct without invading its walls, indeed, this is usually the mechanism of transfer, as cancerous lymphangitis was considered by Troisier to be quite rare. He commented on the predilection for such metastases to occur on the left side, and offered a correct explanation through the anatomic relationship of the left supraclavicular node with the termination of the thoracic duct at the confluence formed by the jugular and supraclavicular veins. He urged the examination of the supraclavicular space in all patients with "organic affections" of the abdomen, observing that in their incipency the metastases in these nodes are noticeable only by palpation and that deformity of the supraclavicular fossa is of later development. The discovery of this left lymph node may bring to light a latent cancer of the stomach or other viscus, which up to then had produced only mild functional disorders. Although the supraclavicular lymphadenopathy is not always a late manifestation and may precede the development of cachexia, it usually indicates an advanced stage or generalization of the cancer. The appearance of the characteristic lymph node contraindicates any attempt at surgical removal of the primary cancer inasmuch as death inevitably ensues within a few months.

A review of the clinical histories of patients with cancer of the liver, small intestine, gall-bladder and urinary bladder has afforded no data concerning the incidence of supraclavicular metastases. This lack of information is not considered significant inasmuch as there are no pathologic or anatomic reasons to support these exceptions. However, the presence of such metastases has been reported by several authors.

Studies have been made with regard to the exact location of the supraclavicular metastases, their anatomic relationship to the region and the method of invasion from the primary tumor. Much practical knowledge of the lymphatics has been secured through clinical and pathologic observations, so in this instance, a proper conception of the lymphatic anatomy of the involved regions will explain the anatomic and physical methods of development of the metastases.

SURGICAL ANATOMY OF THE SUPRA-CLAVICULAR SPACE

The supraclavicular space is made up of vascular and nerve elements separated from the skin by a thin layer of cellular tissue and the superficial cervical aponeurosis and in the most inferior part by the medial cervical aponeurosis which descends from the omohyoid muscle to the clavicle. This constitutes an important clinical and surgical passage which communicates with three regions, the carotid, the axilla and the mediastinum.

From a purely anatomic point of view, the space has three walls or boundaries: an outer one separated by the different superficial planes of the skin and traversed on the inferior part by the omohyoid muscle, a lateral wall comprising the different muscles arising from the cervical column and extending down and outward to the angle of the scapula and the posterior scalenus, and an internal wall with the anterior scalenus muscle as the floor of the compartment. From front to back there are two spaces through which there are ample communications with the posterior mediastinum. The supraclavicular vein passes through the anterior hiatus. The superior scapular artery, the phrenic nerve, the supraclavicular artery and the different branches of the brachial plexus pass through the posterior hiatus. The first rib divides the base of the supraclavicular fossa into two portions: an external segment which is continuous with the apex of the axilla and through which the neurovascular bundle of the subclavian vessels and brachial plexus pass, and the internal segment which is an upward extension with the superior orifice of the thorax and communicates with the apex of the lung, the

pleural space and the fibromuscular tracts which form the suspensory ligament of the pleura.

The contents of the supraclavicular fossa are composed of the important arteries, veins and nerves which come from the neck and body, the brachiocephalic on the right and the subclavian artery with its different branches and the distant part of the descending aorta on the left, the phrenic nerve, and the brachial plexus. A layer of fatty cellular tissue surrounds the vascular and nerve elements and serves to nourish and sustain them where they join the areolar cellular tissues of the carotid region within and below with that of the mediastinum, and below and outward with that of the axilla. In this fatty cellular tissue are found, in addition, the deep lymph nodes of the supraclavicular space, the terminal branches of the lymphatic system, the great lymphatic vein on the right and the thoracic canal or duct on the left.

The great lymphatic vein collects the lymph from the right half and supradiaphragmatic portion of the chest, its termination has many variations. The thoracic duct collects the lymph from all of the left supradiaphragmatic portion of the chest, running from below upward through the posterior mediastinum to the level of the seventh cervical vertebra, where it reverses its direction in a terminal descent. The caudal portion of the duct is commonly formed by the union of three trunks, one on each side which drains the lumbar lymph nodes and a middle third which constitutes the intestinal trunk. The intestinal trunk is formed by the union of efferent lymphatic vessels from the mesenteric lymph nodes and the celiac lymph nodes. The origin of the thoracic duct is often in a dilated portion of the duct known as the cistern of Pequet or cisterna chyli. After the formation of the short descending cervical portion, the duct ends in the internal jugular vein, or in the jugulosubclavian junction itself or occasionally in the left subclavian vein. The termination of the thoracic duct opens in several ways (Buy and Argand). Whenever it opens directly into the vein, perpendicular to the direction of the blood current, the orifice is supplied with two competent valves, in other instances the thoracic duct opens into the venous trunk obliquely by traversing the wall of the vein in such a way that the thoracic duct is compressed by the distention of the vein, which ordinarily renders impossible a reflux of blood into the thoracic duct (Rouviere).

The fatty cellular tissue of the supraclavicular space also surrounds a great number of deep lymph nodes in this region, into which empty efferent lymphatic vessels from the head and

neck. Invasion of these lymph nodes by cancers of the oral cavity, pharynx, larynx and sinuses is well known.

The lymph nodes or signal nodes in which we are interested are the left supraclavicular or deep inferior cervical node, the efferent branches of which enter the terminal part of the jugular trunk, and the right supraclavicular node situated in a similar position with regard to the right great lymphatic vein and its three branches of origin. It should be restated here that these great lymphatic trunks do not empty directly into the signal nodes, the only communication is the efferent lymph channel from the node into the major lymph trunk. With this arrangement, the secondary involvement of the node by metastatic cancer from the abdomen or thorax can occur only by some form of retrograde extension (fig 1).

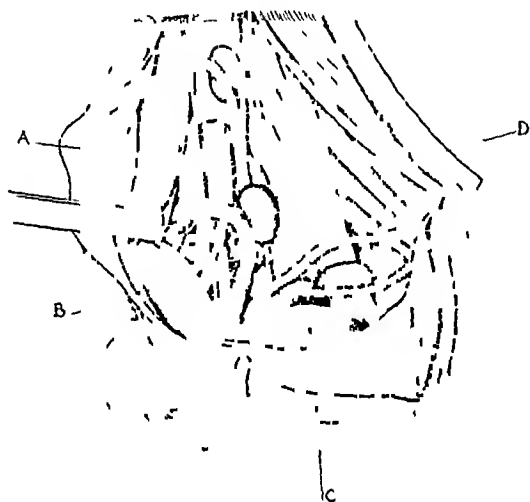


Fig 1—The terminal portion of the thoracic duct. A indicates the jugular vein, B, the thoracic duct, C, the subclavian vein, and D, the sentinel node of Virchow-Troisier. (From Testut, L, and Jacob, O. *Traité d'anatomie topographique avec applications médico-chirurgicales*, ed 2, Paris, Gaston Doin & Cie, 1909, vol 1, p 729, fig 511.)

METHOD OF INVASION OF THE SUPRA-CLAVICULAR LYMPH NODES

The neoplastic cells enter the lymphatic vessels in the vicinity of the primary cancer and are deposited in the lymph node serving as the catchment basin for these particular vessels. The progressive growth of this cancer deposit finally blocks the flow of lymph to the lymph node. The invasion of the more central nodes is accomplished by new emboli from the lymph nodes first invaded and on occasion by infiltration and anastomosis among the lymph nodes. Finally the cancer cells invade efferent lymphatic vessels from the last chain of nodes and these minor trunks are the tributaries of the thoracic duct. By traversing the thoracic duct, the general

circulation is reached with resultant metastases at a distance and especially in the lungs.

The cancer cells travel along the lymphatic vessels as emboli or by infiltration. The theory of embolic spread is most generally accepted, cancer tissue has not always been found in the intermediate lymph vessels and in some instances a cancer has been controlled by treatment directed only to the primary lesion and the metastases without affecting the intermediate tissues, e g, amputation of a toe for subungual melanoma and dissection in the groin for metastatic melanoma.³ The theory of lymphatic permeation championed by Handley⁴ is supported by the result of repeated microscopic studies in which a chain of tumor tissue is sometimes found in the lymphatic vessels following its general direction. Willis⁵ found invasion of the thoracic duct as well as supraclavicular metastases in 13 of 20 patients at autopsy. In 1 patient the obstruction was complete, whereas in others it was limited to the abdominal portion. In 7 patients the thoracic duct was completely free but the tributary abdominal lymph nodes were the seat of metastases which reached the cervical region by embolic transfer.

Willis has emphasized the importance of invasion of the thoracic duct by cancer. In his series of 323 postmortem examinations for cancer, he observed involvement of the thoracic duct in 9 (2.8 per cent) patients, in 147 instances of subdiaphragmatic cancer, the incidence was 6.1 per cent. In cases collected from the literature, Willis found that cancer of the stomach was the diagnosis in 27 of the 81 cases in which invasion of the thoracic duct was discovered at necropsy. The duct may be partially or completely occupied or distended by a solid column of cancer or extensive thrombosis of the lymph in the duct may follow tumor invasion. The presence of cancer in the thoracic duct is an important source of embolic dissemination to the lungs. Visible pulmonary metastases were present in 31 of 81 cases reviewed by Willis and tumor emboli were found microscopically in the additional cases. Cancerous occlusion of the thoracic duct was considered to be the most frequent cause of chylous ascites, but this complication was not always evident.

The direction of the lymph current through the thoracic duct is governed by various factors,

3 Pack, G T, and Rekers, P. The Management of Malignant Tumors in the Groin. A Report of One Hundred and Twenty-Two Groin Dissections, *Am J Surg* 56:545-565, 1942.

4 Handley, W S. Cancer of the Breast and Its Treatment, London, John Murray, 1922, pp 49-63.

5 Willis, R A. The Spread of Tumours in the Human Body, London, Edward Churchill 1934, pp 26-50.

one of which is the state of the valves which are located principally in each extremity of the duct. Insufficiency of the valves in the terminal part of the thoracic duct is only partially corrected by the short distance in which the duct runs parallel to the walls of the vein and blood is commonly found in the terminal part of the duct at autopsy. The principal factor responsible for the flow of lymph in the thoracic duct toward the jugular vein is the negative pressure in the thorax during inspiration.

The isolation of tumor emboli or the partial or total blocking of the duct can change and divert this flow. The emboli may conceivably lodge behind the valves at the termination of the duct and establish small mural tumor thrombi. Obstruction of the thoracic duct at the point of

the thoracic duct as in other lymph vessels is extremely low, therefore a blockage of the channel easily leads to a reversal or retropulsion in the direction of flow, which explains the bizarre metastases sometimes found from cancer of the stomach. Blockage of the terminus of the thoracic duct with resultant stasis of lymph flow may result in retrograde lymphatic permeation, not only of the efferent lymph vessels of the signal node but into other tributary lymphatic vessels of the chest and mediastinum, and of the flow into these collateral channels.

The manner of this invasion has been explained in different ways. Stevens⁶ and Wilks believe that the tumor extends along the thoracic duct and the inferior part of the lymphatic jugular trunk. It has been said that during the act of expiration part of the contents of the duct with the cancer cells can return to the lymphatic jugular trunk and into the efferent vessels of the supraclavicular signal node. Finally, the blocking of the terminal part of the duct could determine the invasion of its wall and the progress of the cancer cells along it in the same direction as the flow or in the opposite direction.

The supraclavicular lymph nodes can be invaded also by way of the efferent vessels of the axillary region, the cancer cells metastasizing from a primary abdominal tumor across the junction of the abdominal wall with the thorax. In a similar way, cancers of the abdominal and thoracic cavities may implicate the mediastinal lymph nodes and ultimately reach one of the two supraclavicular signal nodes. In some of our studies the axillary nodes contained demonstrable metastases prior to the appearance of the signal node, and mediastinal invasion was found in the majority of the autopsies on patients with abdominal cancers metastatic to the signal nodes.

The important role played by the thoracic duct and its relation to the supraclavicular lymph nodes is explained by the fact that involvement of these structures is so frequently encountered. In the 122 patients with supraclavicular metastases in our study, 73 had involvement of the signal node on the left side and 31 of that on the right side and 18 showed bilateral supraclavicular metastases. Invasion of the signal node on the right side which seldom occurs in the case of abdominal cancers is at times explained on the basis of invasion of the mediastinal nodes on this side and in other instances by anastomosis of the thoracic duct with the bronchial lymphatic tree. In thoracic cancer, this association has been found in 51.6 per cent of the cases.

6 Stevens W M. The Dissemination of Intra-Abdominal Malignant Disease by Means of the Lymphatics and Thoracic Duct, *Brit M J* 1 306 310 1907

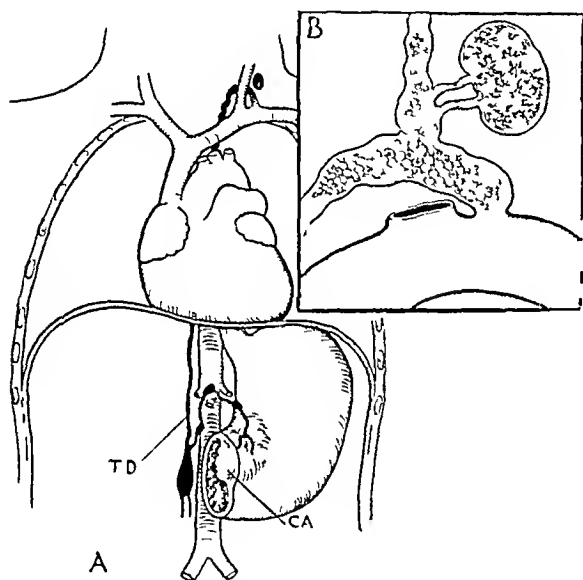


Fig 2—4, mode of transport of cancer emboli from stomach to left supraclavicular signal node. The route is along the different lymph vessels to the perigastric lymph nodes, the coronary, celiac and superior mesenteric nodes. B, way of the truncus intestinalis the emboli enter the cisterna chyli, travel upward along the thoracic duct and enter the systemic venous circulation at the left side of the base of the neck. The sentinel lymph node is shown located behind the sternal head of the left sternomastoid muscle. B, diagram to show involvement of sentinel node by metastatic cancer (Courtesy of Livingston E M. *The Abdominal Cavity and Peritoneum*. New York, Paul B Hoeber, Inc, 1932 p 462 fig 234.)

entry into the jugular vein results in a distention of the efferent lymphatic vessels of the signal node, stasis of lymph and retrograde lymphatic infiltration of the cancer cells into the signal node (fig 2). Whatever the method of invading the thoracic duct may be the mechanism by which the left signal lymph node is involved is a retrograde one going in an almost contrary manner to the lymphatic current of the efferent vessels from the node. The pressure of the lymph in

INCIDENCE OF METASTASES TO SUPRACLAVICULAR SIGNAL NODES FROM ABDOMINAL AND THORACIC CANCERS

Cancers of the various abdominal and thoracic organs do not have the same rate or incidence of metastasis to the signal nodes. One can usually understand the manner of propagation in each instance by studying the histologic nature of the primary tumor and its grade of malignancy along with its anatomic relation to the organ and lymphatic ducts. A more detailed discussion of these observations and the manner in which the metastases reach the supraclavicular lymph nodes follows.

Supraclavicular Metastases from Primary Malignant Tumors of the Stomach—A long time ago the presence of a hard lymph node in the left supraclavicular fossa was described with frequency in association with carcinoma of the stomach. To this phenomenon was attributed a diagnostic significance and prognosis which, in

clavicular region had had two years of local radiation therapy without discovery of the primary tumor. At the end of two years of this satisfactory palliation a tumor of the stomach was discovered on roentgen examination. Roentgen therapy directed at the stomach prolonged this patient's life for an additional two years. Necropsy revealed a liposarcoma in the stomach with diffuse metastases to the retroperitoneal peripancreatic, mediastinal, axillary, femoral and supraclavicular lymph nodes.

The gastric lymphatic vessels drain into four major groups of perigastric lymph nodes, here the metastatic gastric cancer may remain localized for a limited time, sufficient in many instances to permit a surgeon to employ radical surgical treatment. The secondary echelon of lymph nodes involved from gastric cancer are the hepatic nodes, the para-aortic lymph nodes and the nodes in the region of the celiac axis. When the cancer involves the secondary lymph

The Incidence of Supraclavicular Metastases from Abdominal and Thoracic Cancers

Location of Primary Cancer	Number of Cases Examined	Number of Supraclavicular Metastases	Percentage of Supraclavicular Metastases	Supraclavicular Nodes First Sign of Cancer	Supraclavicular Nodes on and After Admission	Location of Supraclavicular Metastases		
						Left	Right	Bilateral
Total	4,365	122	2.8	41	81	73	31	18
Lung	334	44	13.2	11	33	18	15	11
Esophagus	210	15	7.1	2	13	0	8	2
Stomach	883	23	2.6	17	6	15	3	5
Pancreas	37	3	8.1	1	2		3	
Kidney	58	4	6.9	1	3	4		
Ovary	148	9	6.1	4	5	9		
Corpus uteri	336	5	1.5	1	4	5		
Cervix uteri	882	7	0.8	1	6	6	1	
Prostate	104	2	1.9	1	1	1	1	
Testicle	166	8	4.8	1	7	8		
Rectum	928	2	0.2	1	1	2		
Small intestine	54	}	No supraclavicular metastases discovered in the records of patients with tumors of these organs					
Gallbladder	17							
Urinary bladder	208							

Cancers of the lung and esophagus from the service of Dr. William L. Watson; cancers of the kidney, prostate, testicle and urinary bladder from the service of Dr. Archie L. Dean, Jr.; cancers of the ovary, corpus uteri and cervix uteri from the service of Dr. Howard Taylor, Jr.; cancers of the rectum from the service of Dr. George Binkley; and cancers of the stomach, pancreas, small intestine and gallbladder from the service of Dr. George T. Pack.

reality, is of value not only for tumors of this organ but also for any abdominal or thoracic cancer. In 883 patients with gastric cancer there have been only 23, or 2.6 per cent, with supraclavicular metastases. In 15 of these patients the metastasis occurred in the left signal node, in 3 patients the metastasis was on the right side, and in 5 patients both supraclavicular fossae were involved. It is extremely unusual for gastric cancer to metastasize to the right supraclavicular space. In one particular instance recorded here, necropsy revealed metastatic invasion of the mediastinal lymph nodes and carcinomatous lymphangitis of the lungs. Two of the patients came to the hospital complaining of the enlarged signal node as the sole manifestation of their disease. One 34-year-old patient who had metastasis to the left supra-

clavicular region had had two years of local radiation therapy without discovery of the primary tumor. At the end of two years of this satisfactory palliation a tumor of the stomach was discovered on roentgen examination. Roentgen therapy directed at the stomach prolonged this patient's life for an additional two years. Necropsy revealed a liposarcoma in the stomach with diffuse metastases to the retroperitoneal peripancreatic, mediastinal, axillary, femoral and supraclavicular lymph nodes.

The lymphatic drainage of the superior half of the head of the pancreas occurs into the lymph nodes along the pancreaticoduodenal artery, reaching the hepatic and celiac groups of lymph nodes. Other lymphatic vessels drain the inferior portion of the head of the pan-

Supraclavicular Metastases from Primary Cancer of the Pancreas—Carcinoma of the pancreas metastasizes to various groups of lymph nodes in the advanced stages of the disease. Bard and Pic noted a long time ago that the primary tumor may be quite small while the regional metastases may grow to a large size.

The lymphatic drainage of the superior half of the head of the pancreas occurs into the lymph nodes along the pancreaticoduodenal artery, reaching the hepatic and celiac groups of lymph nodes. Other lymphatic vessels drain the inferior portion of the head of the pan-

the body of this organ into lymph nodes in the inferior mesenteric chain of lymph nodes. The lymphatics from the tail of the pancreas empty into lymph nodes associated with the splenic vessels until they ultimately relay into the celiac lymph nodes. By this route it is possible for cells to be transported to the cistern of Pequet and thence to the thoracic duct and left supraclavicular space.

However, among the patients in this series (37) with carcinoma of the pancreas, there were only 3 instances of involvement of the signal nodes, or 8.1 per cent, and all 3 of these cervical metastases were localized in the right supraclavicular fossa. Metastasis to the signal node on the right side was readily explained in 2 instances by anastomosis between the abdominal organs and the nodes of the axillary region, the efferent lymphatic vessels of which led to the inferior segment of the neck. In these 2 patients the axillary metastases were discovered before the appearance of the signal nodes in the right supraclavicular space.

The time of appearance of the signal node in one patient was five months after recognition of the primary pancreatic cancer, in another patient an aspiration biopsy of the signal node led to the investigation which revealed the presence of the tumor in the pancreas, and in the third the site of the primary tumor was discovered only at autopsy.

Supraclavicular Metastases from Primary Cancer of the Esophagus—In 210 patients who died from carcinoma of the esophagus 15, or 7.1 per cent, were found at necropsy to have supraclavicular metastases. The signal node was obviously involved by metastatic cancer in 6 patients who came to the Memorial Hospital complaining only of dysphagia. In 7 other patients metastatic involvement of the signal node occurred during the final stages of the disease. There were 2 patients whose chief complaint was the presence of enlarging supraclavicular lymph nodes, these patients had no symptoms referable to the esophagus, yet esophagoscopy revealed the primary tumor to be situated in both instances on the anterior wall of the esophagus. The localization of the supraclavicular metastases in carcinoma of the esophagus was on the right side in 8 cases, on the left in 5, and bilateral in 2 instances. The situation of the primary tumor in the esophagus may not be of great importance so far as the frequency of metastasis to signal nodes is concerned, for example, 6 of the cancers were in the inferior third of the organ, 5 in the superior and 4 in the middle third. The relative infrequency of involvement of the signal nodes in cancer of the

middle third of the esophagus may be explained in part by the great rapidity with which these tumors grow in this location with direct extension to the mediastinal lymph nodes, the great vessels and the respiratory system, with consequent early termination before sufficient time has elapsed to permit metastasis to lymph nodes at a distance.

Lymphatic invasion by esophageal cancer has been studied in the Memorial Hospital by Watson,⁷ who found that it occurred in 44 per cent of his patients. The lymphatic vessels of the esophagus follow along the wall for a certain distance before leaving the organ to empty into adjacent lymph nodes. In carcinoma of the cervical part of the esophagus metastases occur first into the deep anterior paratracheal lymph nodes and then the internal jugular lymphatic chain. Cancer of the midthoracic portion of the esophagus ultimately metastasizes to the mediastinal and tracheobronchial lymph nodes and to lymph nodes scattered along the posterior wall of the esophagus and then to the supraclavicular spaces. Esophageal cancer involving the inferior third metastasizes into the posterior parietal lymph nodes, the diaphragmatic nodes and the lymph nodes in the region of the celiac plexus. Whatever the location of the primary esophageal cancer, the signal nodes in the neck may ultimately be implicated.

The progress of the cancer after the appearance of the supraclavicular metastases has been rapidly fatal, only 2 patients lived a year.

Supraclavicular Metastases from Primary Cancer of the Rectum—Involvement of the signal nodes by metastasis from cancer of the rectum is a great rarity, as judged by the instance of its occurrence in the group of cases from the Memorial Hospital. Of 928 rectal cancers only 2, or 0.2 per cent, metastasized into the left supraclavicular lymph nodes. In 1 patient the significant enlargement of the node was discovered five months after a primary, inoperable rectal cancer had been diagnosed. In the second patient, a rapidly enlarging signal node was found to be developing two years after the primary cancer of the rectum had been apparently controlled.

Lymphatic extension of rectal cancer as a rule is more or less limited to the lymph nodes of the anorectal group, the hypogastric lymph nodes and others situated near the origin of the sigmoidal vessels. Metastases at a distance from the primary rectal cancer are of late occurrence, and when they do occur there is usually clinical evidence of visceral involvement through the blood stream.

⁷ Watson W. L. Carcinoma of the Esophagus, Surg. Gynec. & Obst. 56: 884-897, 1933.

Supraclavicular Metastases from Primary Malignant Tumors of the Kidney—Four, or 6.9 per cent, of the 58 patients with malignant tumors of the kidney had demonstrable involvement of the supraclavicular lymph nodes. In these 4 patients pathologic study revealed two of the tumors to be adenocarcinoma, one to be an epidermoid carcinoma of the renal pelvis, and the final one Wilms's embryonal adenomyosarcoma occurring in a child 3 years of age. In all patients the cervical localization was on the left side, and only in the case of the epidermoid carcinoma of the renal pelvis was the primary tumor undetected before demonstrable appearance of the signal node in the neck. Malignant tumors of the kidney more frequently metastasize to the lungs, liver and bony structures than they do to regional lymph nodes, yet in the 4 patients listed here there were no clinical evidences of pulmonary, hepatic and osseous metastases, such as are commonly found. These 4 patients died two years, five months, eight months and five months, respectively, after the demonstrable appearance of metastases in the signal nodes.

Supraclavicular Metastases from Primary Cancer of the Prostate—Supraclavicular metastases from malignant tumors of the prostate were found in only 2, or 1.9 per cent, of the 104 patients studied in this review. In 1 patient the metastasis appeared in the left signal node seven months after the primary prostatic cancer had been treated. In the other patient the first sign of cancer was the appearance of a hard firm lymph node in the right supraclavicular space, the diagnosis of cancer was made on biopsy of aspirated material. This led to a general physical examination and discovery of a primary tumor in the prostate.

Various anatomic studies have stressed the mode of metastasis from cancer of the prostate. Metastases at a distance usually occur through the venous system, for example, Batson⁸ emphasized the role played by the vertebral veins in metastases to bone found in 70 per cent of the patients who had carcinoma of the prostate. Extension by way of the lymphatic system is quite variable and generally remains localized to lymph nodes within the pelvis. These metastases occur in order of frequency to the hypogastric lymph nodes, the iliac, para-aortic and inguinal lymph nodes, the extension to the thoracic and cervical lymph nodes is a later relay after invasion of the para-aortic group.

The 2 patients in this series showing involvement of the signal nodes died twenty-one and fourteen months, respectively, after the appearance of demonstrable metastasis in the supraclavicular space, at the time of death both patients had widespread osseous metastases.

Supraclavicular Metastases from Primary Malignant Tumors of the Testicle—In a group of 166 patients with malignant tumors of the testicle supraclavicular metastases were found in 8, or 4.8 per cent. In these 8 patients 3 had embryonal carcinomas and 5 adult teratomas. In all instances the metastasis occurred in the left supraclavicular fossa, and in only 1 patient did enlargement of the signal node appear as the initial evidence of the disease. In 1 phenomenal case the metastasis in the supraclavicular signal node appeared twelve years after orchidectomy.

The embryonal carcinomas and chorioepitheliomas of the testis are highly malignant and spread rapidly through both venous and lymphatic channels, whereas the adult teratomas are inclined to metastasize at a later date and more commonly extend via the lymph vessels. The route of metastasis for malignant tumors of the testicle, then, is through either the blood stream or the lymphatic system or both at the same time. The pre-aortic group of lymph nodes is a most important one. The inguinal lymph nodes are invaded only when the primary tumor of the testis extends directly to the scrotal skin. The first nodal metastases appear as a rule in the upper part of the abdomen. Invasion of the superior pre-aortic lymph nodes affords an explanation for the relatively high percentage of cases with metastases to the mediastinal lymph nodes followed by invasion of the thoracic ducts and finally involvement of lymph nodes in the supraclavicular fossa. Ferguson⁹ reviewed the localization of metastases in autopsies on 45 patients who died of malignant testicular tumors, he found epigastric metastases in 39 instances, mediastinal involvement in 11, and metastatic invasion of supraclavicular signal nodes in 6 patients.

Supraclavicular Metastases from Primary Carcinoma of the Ovary—Among 148 patients who had primary ovarian cancers, 9, or 6.1 per cent, had metastasis in the supraclavicular lymph nodes. In all 9 patients localization of the supra-vascular metastasis was on the left side, in 4 the presence of the cryptic hard node was the initial sign or evidence of disease which prompted the patient to consult a physician. In 1 instance the

8 Batson, O. V. The Function of the Vertebral Veins and Their Role in the Spread of Metastases, *Ann Surg* **112** 138-149, 1940.

9 Ferguson, R. S. Studies in Diagnosis and Treatment of Teratoma Testis, *Am J Roentgenol* **31** 356-365, 1934.

Examination of the supraclavicular lymph nodes should proceed in an orderly fashion by careful inspection and palpation to note any defect or distortion in the development of the skin and the localization, size, movability and consistency of the tumors. Biopsy on tissue aspirated with a 17-gage needle inserted under negative pressure and with local anesthesia may solve the problem of establishing a pathologic diagnosis. In a series of 122 patients with involvement of the signal nodes by metastatic cancer in this series such biopsy was successful in obtaining a representative specimen of tissue in approximately 85 per cent of instances. Biopsy on aspirated tissue should not be relied on for the diagnosis of a tumor of the lymphoma group. Whenever the results of such biopsy were inconclusive and the general physical examination did not offer a satisfactory explanation as to the nature and origin of the disease, a formal biopsy on excised lymph node was carried out.

From a practical point of view the patients with metastatic cancer involving supraclavicular signal nodes can be separated into two groups: (a) those with a known primary cancer at the time of admission and those with a primary cancer easily found at the time of the initial examination, but undetected by the patients, and (b) a group with obvious involvement of the signal nodes by cancer metastatic from an undetermined primary site. In the latter circumstance, the examiner who is familiar with the significance of the supraclavicular signal nodes in patients with cancer of the head and neck, breast, thorax and abdomen will proceed to a detailed investigation in order to rule out or detect the presence of malignant tumors of the head and neck, breast, the upper extremities, the skin and trunk, and will continue with the methodical exploration of the different organs of the abdominal and thoracic cavities from which cancer is capable of metastasizing to the cervical lymph nodes. A pathologic diagnosis of metastatic adenocarcinoma or epidermoid carcinoma aids the clinical investigation considerably by determining a definite organ or system.

Cervical dissection of supraclavicular metastases from primary cancers of the abdomen or thorax is certainly contraindicated. When this region is secondarily involved the cancer is out of surgical control and other metastases at a distance give a poor prognosis and shorten the life of the patient. In the case of malignant tumors of the head and neck removal of the supraclavicular lymph nodes and radical dissec-

tion in the neck comprise a rational procedure, this is also true in the case of certain malignant tumors of the skin, notably melanomas and epidermoid carcinomas situated on the superior part of the body and shoulders. Even in cancer of the breast Halsted had at one time practiced a continuation of the axillary dissection into the supraclavicular space, but today most surgeons operating for mammary cancers consider the involvement of supraclavicular lymph nodes as constituting an inoperable stage of the disease.

The only treatment considered worth while for metastases to the signal nodes secondary to abdominal or thoracic cancer is external irradiation by means of high voltage roentgen rays or the 4 Gm radium element pack. As the treatment is palliative rather than curative it is difficult to evaluate the advantages of the various modalities of irradiation, but the clinical impression exists on a review of the end-results obtained that the radium element pack has proved superior to the ordinary high voltage roentgen rays and the manner of their application in the treatment of supraclavicular metastases. At times a complete regression of huge deposits of metastatic cancer in the supraclavicular space has been obtained with a worth while disappearance of the signs of pressure on the blood vessels draining the upper extremity, and relief of pain from pressure against or invasion of the brachial plexus has been secured. Interstitial irradiation by the deposition of gold radon seeds into the supraclavicular lymph nodes either with or without surgical exposure by incising the skin is contraindicated, although this treatment has been used in a number of cases in this series. Inasmuch as the purpose of the radiation therapy is to secure the utmost in palliation, this objective is defeated when interstitial irradiation is employed, because of the frequent intractable brachial neuritis which may ensue.

As for the ultimate or far reaching end results, such treatments are designed only to relieve pain and discomfort. They have not modified the course of the disease as far as the duration of life is concerned, because this end result is governed solely by the location, the characteristics and the degree of malignancy of the primary cancer and by other metastases which already exist as a rule in other parts of the body.

SUMMARY

Invasion of the supraclavicular lymph nodes from abdominal and thoracic cancers is relatively rare. In a group of 4,365 patients treated for these cancers in the Memorial Hospital only 122 or 2.8 per cent, were found to have involvement of the signal nodes.

The greater frequency of metastases to the left side (59.8 per cent) is explained by the relationship of the thoracic duct with the supraclavicular nodes on this side. Metastatic involvement of lymph nodes in the right supraclavicular space (25.4 per cent) is less frequent and occurs mainly in patients with tumors of the thoracic cavity. Bilateral invasion of the supraclavicular nodes (14.8 per cent) is also more commonly associated with thoracic than with abdominal cancer.

In 81 patients, the signal nodes were invaded only in the advanced stages of the cancer and

in the majority at the same time generalized metastases appeared in other organs.

In 41 patients, the supraclavicular metastases constituted the first clinical sign of a malignant tumor and led to a search for the primary site of the cancer. Aspiration biopsy was a valuable aid in the solution of these diagnostic problems.

Palliative treatment by irradiation improved the local or supraclavicular condition and at times controlled the primary cancer for a certain length of time without appreciably increasing the length of life.

ampere, so that for twelve recording systems a current of 0.6 ampere is needed. This power is required for about one second of each one minute cycle. It can therefore be produced either by using a rectifier dimensioned for the average amperage (in which case the smoothing filter is dimensioned for full power) or by having the timing impulse reach, in succession, one counter after another. In this case the rectifier as well as the smoothing filter can be dimensioned for the power consumption of only one message register.

By use of such an apparatus quantitative data can be obtained on all aspects of the enzymic

digestion of absorbable sutures, and results can be related to the duration of tensile strength of the sutures in the tissues. It should be pointed out that this apparatus is equally suitable for the study of the enzymic digestion of other natural and synthetic protein and carbohydrate fibers.

SUMMARY

The automatically recording apparatus described has been found suitable for measuring the rate of enzymic digestion of absorbable surgical sutures and other protein fibers.

Massachusetts Institute of Technology, Cambridge, Mass.

DREPANOCYTOSIS (SICKLEEMIA) AND AN APPARENTLY ACUTE SURGICAL CONDITION OF THE ABDOMEN

REPORT OF THEIR OCCURRENCE IN A WHITE YOUTH, WITH LAPAROTOMY

CHARLES B CANBY, M D , GURTH CARPENTER, M B, M R C P, AND
LEWIS F ELLMORE, M D

LOS ANGELES

In the classic case of sickle cell anemia described by Herrick¹ the patient suffered from attacks of abdominal pain, a feature now known to be characteristic of the syndrome. In several recorded instances such pain has been sufficiently severe that, together with physical findings, it has led to laparotomy. However, this occurrence is of some rarity, and has not previously been reported in a Caucasian. The case to be reported here is that of an American-born youth of pure Sicilian stock in whom an acute abdominal syndrome led to laparotomy with splenectomy. The history of the case merits recording in view of its import in the differential diagnosis of an acute surgical condition of the abdomen.

REPORT OF A CASE

History—S M., a youth 19 years of age, was admitted to the Los Angeles County General Hospital on Nov 15, 1942. While driving from New York to Los Angeles the patient was awakened at 3 a. m. on November 13 by severe pain in the left side of the abdomen, constant and not radiating. Soon after the onset of pain some alkaline medication was vomited, and there had been some subsequent vomiting, though it was thought that a portion of the fluids ingested was retained. Despite the pain, it was thought best to drive to Los Angeles. The patient was admitted to the Los Angeles County General Hospital approximately forty-eight hours after the onset of pain. The bowels had not moved for three days. Little gas had passed by rectum. The patient complained of a tender swelling in the left side of the abdomen, with some relief on drawing up the left leg. There had been slight dysuria, but no noted change in the urine. There had been no chills and no known fever, nor had there been excessive sweating. The patient had had "the usual diseases of childhood." He was regarded as previously always healthy. There had been occasional "rheumatism" in both legs, but never severe pain.

Postoperatively the history was amplified. The patient had been pale all his life and at different times had noticed some yellowness of the eyes. For the last few months he had been aware of a mass on the left side, but apart from twinges of pain occasionally, it had not

troubled him, and he had accordingly thought nothing of it.

Physical Examination—The temperature was 100.6 F., the pulse rate 102 and the respiratory rate 30. The blood pressure was 118 systolic and 70 diastolic. The appearance was that of a chronically ill, debilitated youth in acute abdominal distress. The skin was pale and sallow but not jaundiced. The scleras were not icteric. The pupils reacted to light and in accommodation. The teeth showed extensive caries, and the mouth was dry, with a furred tongue. There was anterior cervical lymphadenopathy, but no other nodes were enlarged. The lungs were clear. The apex beat of the heart was in the fifth intercostal space outside the midclavicular line. Percussion revealed an enlarged heart, and there was a soft apical systolic murmur propagated to the axilla. The aortic and pulmonic second sounds were of equal intensity.

The abdomen was scaphoid. There was some guarding but no localized rigidity. On the left side at the level of the umbilicus a mass measuring about 3 by 5 cm. was visible, it moved with respiration and on palpation was exquisitely tender. Peristalsis was hypoaactive. There was tenderness in the left costovertebral angle. Rectal examination revealed exquisite tenderness on the left side at the tip of the finger, which did not reach the mass.

The skin of the shins showed no scars. Other findings were not abnormal.

There was no sugar or protein in the urine, an occasional pus cell was present. Examination of the blood on December 15 revealed 15,050 white blood cells, with a differential count of 85 per cent polymorphonuclears and 15 per cent lymphocytes. An erythrocyte count was not made. A roentgenogram taken on the same day showed the pulmonary fields essentially clear, the cardiac silhouette within normal limits and no evidence of subphrenic air. In the abdomen there were several loops of gas-filled bowel, consistent with commencing ileus. The peritoneal borders were indistinct, and there was a general haze over the abdomen suggestive of intraperitoneal fluid.

The clinical impression was that the patient possibly had splenic torsion or volvulus of the small intestine.

Operation—In view of the slight fever, the leukocytosis, the duration of the symptoms without remission and the exquisite tenderness, it was decided that laparotomy should be performed without delay. Accordingly, with the patient under nitrous oxide-ether anesthesia, the abdomen was opened, and the mass was visualized as a dark red splenic tumor covered with fibrin and showing also older fibrous adhesions to surrounding structures. In view of the obviously pathologic nature of the organ, its removal was decided on. The splenic artery was tortuous, but neither artery nor vein was

From the Departments of Medicine and of Surgery the University of Southern California School of Medicine.

¹ Herrick, J. B. Peculiar Elongated and Sickledaped Red Blood Corpuscles in a Case of Severe anemia, Arch Int Med 6:517, 1910.

thrombosed. The spleen was removed and the abdomen closed without incident. Transfusion of 500 cc of citrated blood was started immediately on completion of the operation.

The immediate postoperative diagnosis was multiple infarcts of the spleen, cause unknown.

The patient was discharged from the hospital without further developments on November 29.

Laboratory Examination—Examination postoperatively on December 17 revealed icterus index (after transfusion) 44 units, serum albumin 4.8 Gm and serum globulin 1.9 Gm per hundred cubic centimeters, and a prothrombin level 45 per cent of normal (normally postoperative levels may be reduced). The urinary reaction for urobilinogen was positive to Ehrlich's reagent at a dilution of 1:40. A blood count showed 4,740,000 red blood corpuscles per cubic millimeter, hemoglobin 12 Gm per hundred cubic centimeters, 23,540 white cells and 313,000 platelets per cubic millimeter and 9 per cent reticulocytes. The differential count revealed polymorphonuclears 86.5 per cent, lymphocytes 4.5 per cent, monocytes 8 per cent, eosinophils 0.5 per cent, basophils 0.5 per cent and nucleated red cells 5 per hundred white cells. The bleeding time was one minute and the coagulation time twenty-five minutes by the oiled test tube method (within normal limits).

On a moist smear 100 per cent cells sickled in twelve hours.

Pathologic Examination of the Spleen—The spleen weighed 830 Gm. Old fibrous tissue and fresh fibrin covered its capsule. The organ was firm and deep red. The cut surface showed scattered areas of irregular outline that were more brownish red than the rest of the pulp.

Microscopic examination showed the sinusoids distended with cells which were all sickle forms. There were areas of acute necrosis of splenic tissue which might contain at their center an arteriole plugged with sickle form red cells. There were other areas of older necrosis with commencing resorption and siderosis, and still other extensive areas of acute hemorrhagic necrosis.

Family Study—The father and mother of the patient were not related and were of unadulterated Sicilian stock. The blood of four sisters, two brothers, the mother and the father did not display any tendency to sickle in twenty-four hours.

COMMENT

This case is of interest in two respects. First it adds 1 more to the still short list of published cases of drepanocytosis in the non-Negro. Secondly, it is the first recorded instance in which laparotomy has been performed on a Caucasian on account of an acute abdominal syndrome in this disease.

The cases of drepanocytic anemia hitherto reported in the non-Negro fall into two groups: first, the group in which it is reasonably certain that no recent inheritance of Negro genetic characteristics had been incurred (Cooley and Lee,² a Greek child, Rosenfeld and Pincus,³ an Italian

child, Sights and Simon,⁴ a white American adult, Haden and Evans,⁵ 2 Sicilian siblings, Weiner,⁶ an Italian child, Pontoni,⁷ a Sicilian, Greenwald and Burnet,⁸ 5 members of a Sicilian family, Clarke,^{8a} 2 Italian siblings, Cook Mack,^{8b} 2 white American siblings), and, second, the group in which the patients came from areas where racial admixtures are admittedly common or the fact of sickling was reasonably certain from the record (Archibald,⁹ Castana,¹⁰ Lawrence,¹¹ Stewart,¹² Wallace and Killingsworth¹³). It is not that a great proportion of the recorded occurrences of this disease in Caucasians have been in persons of Sicilian stock, and it is interesting that, in the United States at least, a high proportion of instances of the familial hypochromic anemia which goes by the name of Cook erythroblastosis is also seen in Sicilian families.

Previous instances of laparotomy on patients with sicklemia have also been recorded by Levy and by Campbell¹⁵ (3 instances). In Levy's case a Negro girl displayed rigidity of the rectus muscle, leukocytosis and fever, with gastric pain and vomiting. Appendectomy was performed. Diagnosis of sicklemia was made one year later when she returned with recurring

4 Sights, W. P., and Simon, S. D. Marked Erythrocytic Sickling in White Adult Associated with Anemia, Syphilis and Malaria. Report of Case, *J. M. A.* **12**: 177-178, 1931.

5 Haden, R. L., and Evans, F. D. Sicklemia in White Race, *Arch. Int. Med.* **60**: 133-137 (July) 1937.

6 Weiner, S. B. Sicklemia in Italian Child, *J. Mt. Sinai Hosp.* **4**: 88-91, 1937.

7 Pontoni, L. Sulla eritropatia drepanocitica costituzionale tipo Herrick, *Haematologica* **20**: 657-724, 1930.

8 Greenwald, L., and Burnet, J. B. Sicklemia in White Family, *Am. J. M. Sc.* **199**: 768-774, 1940.

8a Clarke, F. Sicklemia in White Adult with Report of Two Cases, *Nebraska M. J.* **18**: 379, 1933.

8b Cook, J. V., and Mack, J. K. Sicklemia in White American Family, *J. Pediatr.* **5**: 607, 1934.

9 Archibald, R. G. Sicklemia in Sudan, *Tr. Roy. Soc. Trop. Med. & Hyg.* **19**: 385-392, 1926.

10 Castana, V. I gigantociti e le anemie semilunari, *Pediatrics* **33**: 431-440, 1925.

11 Lawrence, J. S. Elliptical and Sick Shaped Erythrocytes in Circulating Blood of White Persons, *J. Clin. Investigation* **5**: 31-49, 1927.

12 Stewart, W. B. Sicklemia. Report of Case with Splenectomy, *Am. J. Dis. Child.* **34**: 72-73 (July) 1927.

13 Wallace, S. A., and Killingsworth, W. P. Sicklemia in the Mexican Race, *Am. J. Dis. Child.* **50**: 1215 (Nov.) 1935.

14 Levy, J. Sicklemia, *Ann. Int. Med.* **3**: 47-54, 1930.

15 Campbell, E. H., Jr. Acute Abdominal Pain in Sicklemia, *Arch. Surg.* **31**: 607-621 (Oct.) 1935.

2 Cooley, T. B., and Lee, P. Sicklemia in a Greek Family, *Am. J. Dis. Child.* **38**: 103-106 (July) 1929.

3 Rosenfeld, S., and Pincus, J. B. Occurrence of Sicklemia in White Race, *Am. J. M. Sc.* **184**: 674-682, 1932.

abdominal pain Campbell's excellent paper discusses 6 cases of acute abdominal pain, in 3 of which the patients were operated on under conditions of considerable interest All were young Negroes The first exhibited the clinical picture of ileus, and laparotomy with appendectomy was performed, the diagnosis of sickle cell anemia was made two days after operation His second patient, a Negro youngster known to have sickle cell anemia, was admitted to the hospital with severe abdominal cramps, constipation leukocytosis and fever Vomiting commenced, and laparotomy was deemed wise A normal appendix was then removed, and the pain subsided on the third day after operation The third patient who underwent operation was a 36 year old man with a precedent history of three attacks of acute abdominal pain, the first of which had been treated with ice packs, the second by laparotomy and appendectomy and the third by exploratory laparotomy On the occasion of the fourth attack he presented the picture of marked abdominal boarding with leukocytosis, and another laparotomy was undertaken under the impression that peritonitis from a perforated ulcer might be present The abdominal contents were normal except that the spleen was enlarged, and because of this fact the diagnosis of sickle cell anemia was immediately made from fresh smears

It is thus apparent from these and other reported cases that the abdominal syndrome in drepanocytosis may closely simulate a number of patterns of acute abdominal disease Ileus, perforated ulcer, appendicitis, acute cholecystitis and pelvic inflammatory disease appear to be most commonly simulated Splenic pain, presumably due to small infarcts in that organ during the stage of enlargement, is also common, but it does not often reach the severity noted in the case we report It is further apparent from our and from other cases that at the height of the painful episode there may be no anemia, no icterus and no frank sickling of fresh blood Leukocytosis, however, appears to be common, and it is probable that reticulocytosis would be

found to be uniformly present if suitable examination were made In this respect, it should be remembered that the technic of Hansen-Preuss in which an oil-sealed fresh moist preparation is set up on a cresyl blue slide, will bring out sickling in about four hours in cases of the sickle cell trait, and will also demonstrate reticulocytes Such a preparation should be set up immediately when obscure acute abdominal syndromes are encountered in Negroes and in Mediterranean Caucasians

It is also noteworthy that operations for osteomyelitis have been undertaken because of pain in the bones in cases of sickle cell anemia (Dreyfoos¹⁶, Alden¹⁷, Leivy and Schnabel¹⁸)

We are not here concerned with the 10 recorded cases of drepanocytic anemia (see Haden and Evans⁵) in which splenectomy was deliberately undertaken as an experimental therapeutic measure It is known that this operation neither cures the anemia nor prevents the hemolytic attacks, but authors (Haden and Evans⁵, Landon and Patterson¹⁹) have felt that the symptomatic improvement in the anemia and in the frequency of hemolytic or painful episodes justified this undertaking in cases in which there was great splenomegaly Ultimately by repeated infarcts the patients may be said to splenectomize themselves

SUMMARY

The case reported and discussed is the first recorded instance in which laparotomy has been performed on a Caucasian on account of acute abdominal pain caused by the sickle cell trait

16 Dreyfoos M Sickie Cell Anemia, Arch Pediat 43 436-447, 1926

17 Alden H S Sickie Cell Anemia Report of Two Cases from Ohio Illustrating Its Hemolytic Nature, Am J M Sc 173 168-175, 1927

18 Leivy, F E, and Schnabel, T G Abdominal Crises in Sickie Cell Anemia, Am J M Sc 183 381-391, 1932

19 Landon, F E, and Patterson, H A Evaluation of Splenectomy in Treatment of Sickie Cell Anemia Late Results of Two Cases so Treated with Summary of Present Condition of All Splenectomized Patients, J Pediat 7 472-477, 1935

HEMANGIOMA OF THE MEDIASTINUM

REPORT OF A CASE

W E ADAMS, M D, AND R G BLOCH, M D

CHICAGO

Hemangiomas are frequently observed in various tissues and locations in the body. However, a review of the literature revealed but 1 case in which the tumor was located in the mediastinum.¹ This was a malignant hemangioendothelioma occurring in a man. The tumor was removed but the patient died two months after the operation. A postmortem examination revealed some of

CASE REPORT

History—R B, a white man 34 years of age, entered the Frank Billings Medical Clinic because of an unusual opacity in the left pulmonary field on routine roentgen examination at another hospital. The patient had "caught cold" two months before admission and a productive cough had developed. It persisted for about three weeks. Because the cold cough persisted for some time, he went to a pub-



Fig 1—Preoperative roentgenograms of the chest showing tumor extending outward from the anterior mediastinum. Note circular opaque shadow (calcified phlebolith) in line with the left second rib anteriorly. Iodized oil is seen in the left lower pulmonary field.

the primary growth as well as secondary metastases to the lungs.

A monograph on tumors of the mediastinum by Heuer and Andrus² as well as textbooks on thoracic surgery have not mentioned hemangiomas in this location. The following case is reported because of the unusual site and size of the tumor and because of the interesting postoperative course.

From the Departments of Surgery and Medicine of the University of Chicago.

1 Winkelbauer A. Zur Frage der chirurgischen Behandlung der Mittelfellgeschwülste, Wien klin Wchnschr 42 650, 1929.

2 Heuer, G J, and Andrus, W D. The Surgery of Mediastinal Tumors, Am J Surg 50 143 1940.

health clinic for a check-up. Nothing unusual was observed on physical examination at that time, however, a roentgenogram of the chest revealed an unusual opacity in the left pulmonary field. On entering the clinic two months later, the patient's cold had cleared up entirely, and he appeared to have recovered completely. His past history revealed that at the age of 18 months he had had a tumor removed from the base of the neck, on the left side. Again, at the age of 10 years something was removed from the same region. The family history was irrelevant.

Examination—Physical examination revealed a well developed man who appeared to be in good health. The chief findings were as follows. At the base of the neck on the left side, an irregularly shaped rather firm but freely movable nontender mass was palpable. The blood pressure was 130 systolic and 84 diastolic. There was no cardiac enlargement, and the heart tones were normal. An examination of the chest revealed no

asymmetry, however, there was greater expansion on the right side. Tactile and vocal fremitus were almost completely absent over the upper two thirds of the left lung anteriorly and posteriorly. Breath sounds were diminished or absent in the same region. Percussion over this portion of the chest showed dullness to flatness. No rales were audible.

Laboratory examinations showed the blood and urine to be normal. A fluoroscopic examination revealed an



Fig 2—Tumor after sectioning. Note trabecular arrangement of connective tissue around cavernous blood channels. A large phlebolith is seen at A.

opacity in the upper two thirds of the chest, which did not move with the lung on respiration. A roentgenogram added little to the fluoroscopic observations with the exception of several rounded shadows scattered through the opaque region, these were somewhat more dense at the periphery (fig 1). The diagnosis was tumor of the mediastinum of undetermined origin. The nodules within the opaque area were suggestive of hemangioma. A biopsy of the tumor in the neck showed it to be a hemangioma presenting a dense fibrous stroma separating vascular spaces varying in size from that of capillaries to large cavernous sinusoids. All of these spaces were lined with endothelium and some were filled with erythrocytes.

In view of the apparent relation of the intrathoracic mass to the supraclavicular tumor on the left side of the neck, a hemangioma of the mediastinum was strongly considered as the correct diagnosis. Under fluoroscopic control, 20 cc of iodized oil was introduced into the tracheobronchial tree by the aspiration technique. By positioning the patient, the left bronchial tree could be outlined and was found to be displaced posteriorly by a tumor occupying the anterior half of the upper two thirds of the chest. A diagnostic pneumothorax showed the left pleural cavity to be almost entirely free of adhesions with the exception of a few located between the tumor and the diaphragm. The vital capacity

was 3,050 cc. In view of the uncertainty of the diagnosis and the large size of the tumor, it was thought advisable to explore the thoracic cavity.

Operation—On Nov 2, 1939, with the patient under ethylene anesthesia, an exploration was made through a curved incision encircling the lower one half of the left breast, the left pleural cavity being opened through the fourth left inner space. It was necessary to divide the third and fourth costal cartilages near the sternum, the opening being enlarged with a rib spreader. A fairly soft, oblong tumor extended from the first to the seventh ribs anteriorly and from the mediastinum to a point beyond the nipple line. It was partly attached by fairly dense adhesions to the wall of the chest anteriorly and to the lung posteriorly. With relatively little difficulty the tumor was mobilized from the surrounding structures up to the mediastinal attachment. Separation at the mediastinum could not be carried out by blunt dissection, thus the tumor was divided between clamps and sutures. The pedicle of the tumor was broad, measuring about 3 inches (7 cm) in its vertical dimension, and $1\frac{1}{2}$ to 2 inches (4 to 5 cm) anteroposteriorly. It was necessary to leave a small portion of the tumor superiorly, behind the left clavicle. A piece of pericardium measuring 2 by 2 cm, to which it was densely adherent, was removed with the tumor. Closure of the wound in layers was made with chromic catgut sutures.



Fig 3—Roentgen appearance of chest four months after removal of tumor. The left side of the diaphragm is still elevated and some iodized oil remains in the lower lobe of the left lung.

A small mushroom-tipped catheter was brought out through a stab wound in the fifth intercostal space anterolaterally for obliteration of the surgical pneumothorax and for drainage of fluid by constant suction. As the tumor was removed, intravenous introduction of a saline solution was begun and was followed by a transfusion of 600 cc of citrated blood.

Postoperative Course.—The patient was returned to his room in a satisfactory condition. However, because he had lost considerable blood during the operation and because his blood pressure was somewhat lower than normal a second transfusion of 700 cc of blood was given. During the following day, his condition continued fairly good with the exception of a rapid and more or less unstable pulse, the rate being between

talization by intravenous, subcutaneous and oral route was carried out, and nasal administration of oxygen was begun at the rate of 12 liters per minute. With the next three hours, the patient showed signs of improvement, and by the following morning the pulse rate was about 120 to 150, the pulse deficit about 30. The temperature during this time ranged between 99 and 106 F., being around 101 to 103 mc

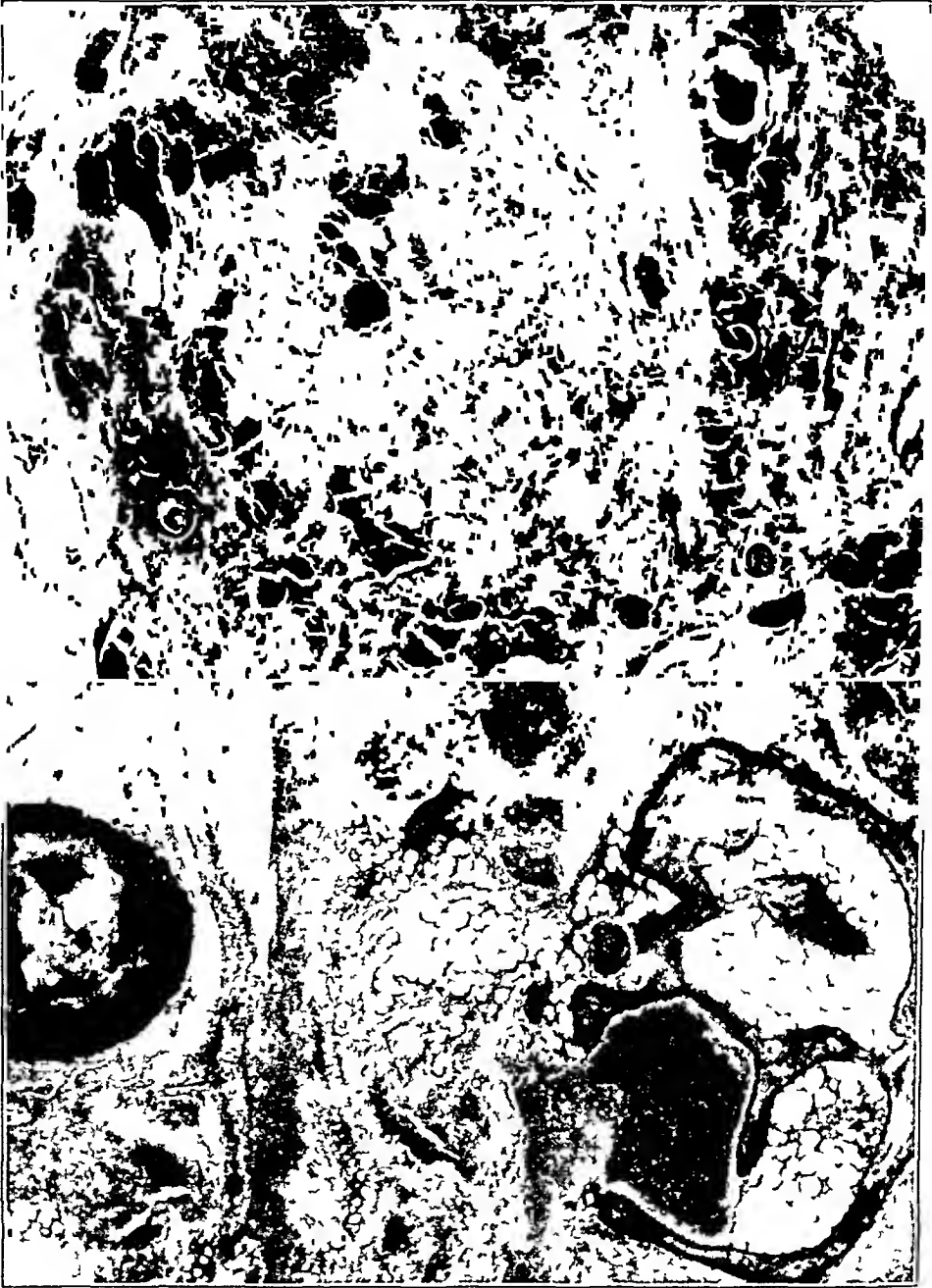


Fig 4—Two magnifications of microscopic sections of tumor. Note numerous large blood spaces distributed throughout the connective tissue framework. A phlebolith and bone containing marrow are seen in the higher magnification.

130 and 160 per minute. There was little drainage from the pleural cavity. On the morning of the third postoperative day, he suddenly became pale and perspired profusely, and an extremely rapid, thready pulse developed. The apex beat obtained with a stethoscope was 300 per minute. Caffeine and sodium benzoate was given but effected little improvement. Rapid digi-

talization of the blood revealed 90 to 100 per cent hemoglobin and 506 million red cells.

The respiratory rate varied from 18 to 28. Little fluid was drained from the pleural cavity. The urinary output was as follows: 750 cc for the day of operation, 500 cc for the second day, 875 cc for the third day and 1320 cc for the fourth day. During this entire

three day period, the patient had few complaints except some "tightness" across the sternum and some epigastric pain localized over the xiphoid process. During the next two days there continued to be some pulse deficit, which had almost completely disappeared by the end of the fifth postoperative day. The patient's temperature gradually returned to normal, ranging between 100 and 102 F for two days and below 100 thereafter. The pulse rate gradually fell to 110 and remained at that level or below thereafter. An electrocardiogram taken on the morning of the sudden collapse (third postoperative day) revealed an auricular flutter with irregular ventricular response. A second electrocardiogram made four days later revealed a sinus tachycardia and some abnormalities due to the administration of digitalis. When repeated three weeks later, there was little evidence of abnormality. The patient gradually improved, but a low grade infection developed in the inner one half of the wound, which necessitated drainage. After several minor operations for the removal of small pieces of infected cartilage, the wound healed and the patient was discharged from the hospital six and one-half weeks after the operation. At the time this paper is written, four years after the operation, the cardiac condition appears to be entirely normal.

Shortly after the operation it was noticed that the patient's voice was somewhat husky. Examination of the vocal cords revealed paralysis on the left side. His voice continued to improve, but recent examination

revealed paralysis and some atrophy of the left vocal cord.

Pathologic Examination—The tumor removed at the operation weighed 527 Gm and measured 18 by 10 by 5 cm. The surface was covered by a somewhat glossy, smooth, soft and thin capsule, through which could be seen many dilated vessels. The freshly cut surface appeared to be cavernous, it was made up of innumerable finely interlaced fibrous trabeculae, and from the spaces between them dark-colored blood could be expressed. Many of these sinuses were filled with what appeared to be dark blood clots, and on palpation several hard spherical nodules were demonstrable. Further sectioning of the tissue revealed that two of the larger nodules or calculi measured about 8 mm in diameter. One was light colored, stony hard and pedunculated. The second was dark brown and extremely friable and was well encapsulated in the tumor mass. Several smaller calculi were found (figs 2 and 4).

A microscopic examination revealed pink-staining fibrous tissue with blue-staining fibroblasts, in which were many foci of lymphocytes. Distributed throughout the tissue were many endothelium-lined blood-filled sinuses and many normal-appearing blood vessels. In some places, irregularly distributed, were areas of aerolar-like tissue infiltrated with lymphocytes. Bone, containing marrow, was seen in two areas (fig 4 B). There was no evidence of malignancy. The final diagnosis was hemangioma of the mediastinum.

CASEIN IN THE LOCAL TREATMENT OF BURNS AND WOUNDS

RAYMOND M CURTIS, M D

AND

JOHN H BREWER, P H D

BALTIMORE

In advocating a local treatment for burns, it is important to take into consideration the way in which the body attempts to seal off the burned areas. This is done by the transudation of a fluid containing plasma protein, and with the evaporation of the water present in this fluid, the protein is left as a protective covering. Petit,¹ in 1915, was one of the first to follow this line of reasoning and suggested the use of horse serum in the treatment of burns and wounds, again, in 1929, Monteith and Clock² described 5 cases of burns treated by this method. Shortell, Cotting and Leary,³ in 1917, first described the use of bovine serum for this purpose. Aside from these few reports there has been little investigation with this approach in mind until recently.

Due to the war it is now essential that we have an agent for treatment for burns that is, in itself, sterile, flexible, easily transported and inexpensive and that can be used by untrained personnel. At the same time it must be adapted to the treatment of superficial as well as deep burns. It must be suitable for use at the first aid dressing stations, in the field and on shipboard, as well as in hospitals. When the war began it became apparent that no method in use at that time satisfied all of these requirements.

A great number of agents for local treatment of burns have been advocated, the majority of which have been a means of converting an open wound into a closed wound at the earliest possible moment. Some of the most widely accepted of these are known as the coagulants, the damage which these agents produce in the denuded area has been pointed out by Allen and Koch.⁴ Wells, Humphrey and Coll⁵ have recently reported central necrosis of the liver due to the toxic action of tannic acid, one of the most popular of these coagulating agents. In the plastic surgery service of the Union Memorial Hospital, both Dr J S Davis⁶ and Dr E A Kitlowski⁷ have been impressed by the amount of damage caused by these coagulating agents, and feel that in many instances a superficial burn is converted

From the Department of Surgery, Union Memorial Hospital, and the Bacteriological Research Laboratory of Hynson Westcott and Dunning, Baltimore.

A resume of this work was presented before the Burn Committee of the National Research Council, Sept 14, 1942 and April 3, 1943 and also before the American Society of Plastic and Reconstructive Surgery, Dec 4, 1942.

1 Petit R. *Les phagocytes en chirurgie*, Paris, Masson & Cie, 1915.

2 Monteith, S R, and Clock, R O. *Treatment of Burns with Normal Horse Serum*, J A M A **92** 1173 (April 6) 1929.

3 Shortell, J H, Cotting, W E, and Leary, T. *The Treatment of Wound with Normal (Beef) Serum*, Boston M & S J **177** 622, 1917.

4 Allen H S, and Koch S L. *Treatment of Patients with Severe Burns*, Surg, Gynec & Obst **74** 914, 1942.

5 Wells, D B, Humphrey H D, and Coll, J J. *Relation of Tannic Acid to Liver Necrosis Occurring in Burns*, New England J Med **226** 629, 1942.

6 Davis I S. Personal communication to the authors.

7 Kitlowski, E A. Personal communication to the authors.

into a deep burn with occasional destruction of the full thickness of the skin. On the other hand, the value of the early eschar treatment of burns is well recognized and has been proved experimentally by Glover,⁸ who has shown that the early precipitation of protein at the site of the burn in the form of an eschar greatly minimizes the protein shift and the resultant hemoconcentration. Superficial burns are minor wounds liberally dotted with islands of epithelium ready to regenerate and cover the denuded areas, unless destroyed by the local treatment or infection. There is no doubt that the burned area requires protection, first to prevent loss of fluid and second to prevent the entrance of pyogenic bacteria. Yet all of this must not be accomplished at the expense of these living islands of epithelium.

Curtis and Worthington,⁹ in 1941, reported the use of human placental plasma in wound therapy. From there this investigation proceeded to the use of adult and fetal bovine serum in a series of 40 cases of burns. During the time we used the serum, it was tried in three forms: (a) as a dusting powder, (b) as an ointment, in a water-soluble base, containing 40 per cent serum and 5 per cent sodium sulfathiazole, (c) as a dried serum, diluted to a protein concentration of 30 per cent (about four times normal) with sterile, distilled water, and sprayed with an atomizer. The object of all three forms was to produce a covering that was bacteriostatic without affecting the tissue proteins themselves. After observing the results obtained with the use of human and bovine serums and the results in some of the early cases with preparations in which the serum proteins were replaced by other materials containing essentially the same amino acids, we came to the conclusion that there was no advantage in using serums for this treatment of burns rather than preparations containing protein from other sources. The difficulties in the preparation of the serum, together with the long drying time when it was applied to the burned surface, caused us to turn to a substitute protein with a short drying time.

Early investigations led us to believe that the ideal type of therapy would consist of a readily available and cheap protein which would closely resemble human plasma protein, or its basic amino acids, to which the human body would show no signs of initial sensitivity and which would not be toxic to tissue cells. This protein should be in a solution which could be applied to the burned area, and which would dry rapidly, covering the denuded surface with a protective film of protein. In this way a film would be formed over the denuded surface and would not require the burned patient to furnish an eschar either in the form of exuded plasma or coagulated cellular protein. After an exhaustive study of the proteins available the most satisfactory preparation was found to be one made from casein. This is a phosphoprotein precipitated from milk by dilute acids and is a readily obtainable and an inexpensive by-product of milk.

The most satisfactory casein preparation which forms its own film has the following composition:

Casein	30 Gm
Sodium lauryl sulfate	4 Gm
50% sodium lactate	10 cc
Sodium hydroxide	0.7 Gm
Water	140 cc

⁸ Glover, D. M. A Critical Evaluation of the Treatment of Burns, *Ann Surg* **113** 1090, 1941.

⁹ Curtis, R. M., and Worthington, R. W., Jr. Placental Blood Plasma, *Am J Obst & Gynec* **42** 428, 1941.

These ingredients are mixed, dissolved and sterilized by autoclaving. In this process, the casein is converted into sodium caseinate and also undergoes some hydrolysis. The final product is a clear, light brown or amber liquid which is sufficiently fluid for application as described hereinafter. The solution after sterilization has a p_H of approximately 8 and is stable at ordinary temperatures when kept in a tightly closed container. When the first casein preparations were made and used clinically, the need for a plasticizing agent became apparent. Preparations containing glycerin, ethylene and propylene glycol, monoethanolamine and triethanolamine were tried clinically, but none was found to be satisfactory. Sodium lactate was found to offer none of the objections of the previously mentioned plasticizers. It is a nontoxic compound and when added to the casein allows one to prepare a solution which dries as a pliable film, not readily cracking or scaling off the burned area.

In the earlier cases we used a preparation which did not contain sodium lauryl sulfate, but did contain 3 Gm. of sulfathiazole and 25 cc. of ethyl alcohol in each hundred cubic centimeters of the solution. This preparation was discarded when it was found that better results were obtained when a plastic film and the solution containing sodium lauryl sulfate was used.

To demonstrate that the casein solution is nontoxic to tissue cells *in vivo*, the following tests were carried out. A donor site from which a skin graft 0.012 inch in thickness had been removed, by means of the Padgett dermatome, was divided into two equal parts. One part was covered with petrolatum gauze, the other with the casein solution, plus the commercially available film described later in this paper. No difference was observed in the length of time necessary for epithelization or in the appearance of the epithelium covering the two areas. Cannon and Cope¹⁴ have proved the value of this standard technic in clinically judging the effect of various substances on the healing of an epithelial wound. Further small deep grafts were buried in the casein solution and kept at 5 C. for twenty-four hours. They were then removed, washed with isotonic solution of sodium chloride and placed on clean granulating areas simultaneously with fresh grafts taken from the patient. No difference was noted in the number of takes or the growth rate in the two instances.

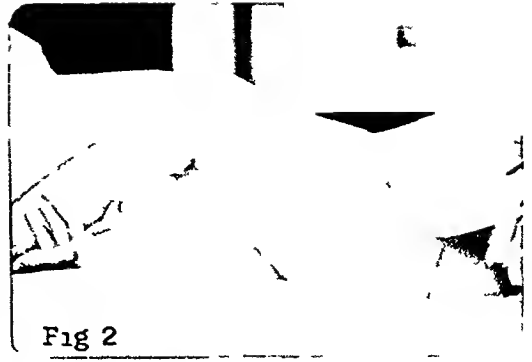
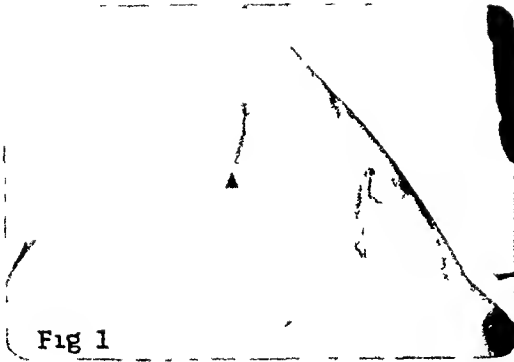
Early in our investigation it became apparent that it would be impossible to develop a protein solution which would dry rapidly on the weeping surface of superficial burns. To overcome this, we clinically experimented with various transparent, commercially prepared coverings, and many of them are usable. We found that one prepared from casein itself was satisfactory, however, it was necessary to renew the film every four to five days when it was used on a badly weeping surface. We also used a film prepared from viscose and found this to be much more satisfactory than the casein film, particularly since it did not necessitate renewal. However, the one which has proved the most satisfactory is prepared from polyvinyl chloride. It is durable, transparent, very soft and flexible and is not permeable to oil or water. It can be used where there is apt to be motion, as over joints. The patient finds the burned areas so comfortable with this dressing in place that he can lie on the burn or walk about. The latter two films are easily sterilized by autoclaving. Pickrell¹⁵ and Andrus, Nickel and Schmelkes¹⁶ have recently reported the use of films of methyl cellulose in burn therapy.

10 Footnotes 10 to 13 were deleted by the authors.

14 Cannon, B., and Cope, O. Rate of Epithelial Regeneration, *Ann Surg* **117** 85, 1943.

15 Pickrell, K. L. A Sulfonamide Film for Use as a Surgical Dressing. Preliminary Report, *Bull Johns Hopkins Hosp* **71** 304, 1942.

16 Andrus, W. DeW., Nickel, W. F., and Schmelkes, F. C. Treatment of Burns with Chemotherapeutic Membranes. *Arch Surg* **46** 1 (Jan) 1943.



EXPLANATIONS OF FIGURES

Fig 1—Photograph of burn on patient's admission to the hospital

Fig 2—Burn debrided, covered with casein solution, film and pressure dressing

Fig 3—Forty-eight hours after the patient's admission the dressing has been removed to show the appearance of the burn beneath the film. There is a central area of deep burn surrounded by a zone of more superficial burn

Fig 4—Fifty days after admission there is complete separation of the dead skin with areas of intact corium

Fig 5—Sixty-five days after admission there are islands of epithelium scattered over the surface of the burn originating from the intact portions of corium

Fig 6—One hundred and twenty-eight days after the burn the area is completely healed. There is very little scar tissue

METHOD OF TREATMENT

With a sterile technic, any loose, necrotic skin is removed. The casein solution is applied to the superficial as well as to the more deeply burned areas with a sterile wooden spatula. Over this solution is then placed the film and several thicknesses of sterile gauze. On suitable large areas, an Ace bandage is applied to exert pressure to the injured area. When the burns are on the face and a rapidly drying film is not necessary, the solution may be used alone. In all erythematous areas it may be used alone because here it dries rapidly. In the deeper burns it is advisable to use the combination of the solution plus a film.

The Ace bandage is used as a means of applying a pressure dressing to the damaged area, for our experience here has shown the value of this type of dressing, particularly when there is injury to tissues as in the case of severe burns. Blair¹⁷ has shown that a dressing with moderate pressure applied over damaged tissue helps prevent the congestion and maintains the circulation in the subcutaneous tissue. Siler and Reid¹⁸ experimentally have shown that the loss of plasma at the site of, and into the surrounding tissues of, burned areas can be reduced by primary pressure dressing.

RESULTS OF TREATMENT

To date 165 cases of burns and 75 cases of wounds have been treated in the manner described, 43 of the cases of burns being severe enough to necessitate hospitalization. One case is illustrated and described in detail.

Clinical Course of Patient

Date	Hour	Rectal Temperature F	Pulse Rate	Hemato crit, per Cent	Fluid Intake	Urinary Output
12/28	12 50 p m	100	100	50	1 500 cc plasma intravenously	
	8 00 p m	100	120	50	500 cc plasma intravenously 1 000 cc 5% dextrose in distilled water intravenously	
12/29	12 00 a m	100	120	50		
	8 00 a m	100.4	120	57	750 cc plasma, 1 000 cc 5% dextrose in distilled water intravenously 670 cc orally	600 cc
12/30	8 00 a m	103	130	45	2 100 cc 5% dextrose in distilled water intravenously 1 800 cc orally	1 200 cc
12/31	8 00 a m	101	120		900 cc 5% dextrose in distilled water intravenously 2 105 cc orally	2 100 cc

REPORT OF A CASE

H S., a white woman, aged 34, was admitted to the Union Memorial Hospital on Dec 28, 1942, three hours after setting fire to her hair. First aid consisted of sterile dressings to the burned areas prior to admission and morphine, $\frac{1}{4}$ grain (0.015 Gm), hypodermically on admission. The blood pressure was 148 systolic and 90 diastolic, the pulse rate 100. Examination revealed burns of the entire head, the back of the neck to the shoulders and the face, which appeared to involve the full thickness of the skin, except those around the eyes and nose, which appeared to be superficial. There was a burned area consisting of two thirds of the left thigh involving the full thickness of the skin and similarly one of 6 cm in diameter on the right thigh. The total area involved as estimated by the Berkow scale was 20 per cent of the body, with 15 per cent of this being deep burns. The patient was placed on sterile sheets and the technic already described was used on all areas except the scalp and eyelids. Because some hair remained on the scalp only sterile gauze and an Ace bandage was applied there, and due to the great edema of the eyelids sterile boric acid compresses were used. The clinical course with reference to the hematocrit and fluid given intravenously during the first four days is shown in the table. On December 29, the general

17 Blair, V P. Influence of Mechanical Pressure on Wound Healing, Illinois M J 46 249, 1924

18 Siler, N E, and Reid, M R. Clinical and Experimental Studies with the Koch Method of Treatment of Heat Burns. Ann Surg 115 1106, 1942

condition was improved except for difficulty in breathing due to edema of the larynx and trachea. This was relieved by inhalations of compound tincture of benzoin. Administration of sulfadiazine was started and a blood level of 38 mg per hundred cubic centimeters was maintained for eleven days. On January 3 and 10 the casein film and the solution on the burn on the left thigh were renewed. On January 14, Dr Kitlowski, under ether anesthesia, removed the dressing and the film from the face, neck and shoulders and debrided these areas and applied Ollier-Thiersch grafts. On February 17, more Ollier-Thiersch grafts were applied to several areas on the neck and face. Inspection of the area on the thigh after the first two weeks revealed that in some parts the full thickness of the skin was not destroyed, and the progress of this area is illustrated. The patient's convalescence was uneventful, with the temperature ranging from 98.6 to 100 F.

This case clearly points out the importance of the local use of an agent which is nontoxic to tissue cells. In figure 5 one can see the islands of epithelium beginning to appear in areas where the full thickness of the skin was thought to have been destroyed. These areas, which appear like small grafts, have developed from a part of the corium which was not destroyed by the burn. They would undoubtedly have been destroyed by the toxic agents which are often applied to the burned surface.

The results obtained in burns with this treatment for ambulatory, as well as hospitalized, patients has been most gratifying. In only 2 cases of burns was there evidence of infection beneath the film when the patient received immediate treatment. In 1 patient treated twelve hours after being burned, some infection developed on the fourteenth day, when an area of tissue, whose depth of destruction extended to the subcutaneous fat, began to separate. The treatment was used in 2 other cases in which the patient was admitted to the hospital grossly infected seventy-two hours after being burned, treatment at home having consisted of the application of lard. In the latter 2 cases the solution was applied after thorough cleaning of the area. In three days, when we saw evidence of infection beneath the clear covering, these areas were compressed for several hours and the casein film was easily removed and the solution reapplied. Many of the burns were chemical burns produced by fluorides. These areas heal rapidly under this treatment. In several of the patients the burns extended over the face and even into the hair or onto the fingers, and this therapy was found to be of equal value here. The casein solution when dry forms a film which is very flexible and does not contract. These two features make it valuable in the treatment of burns in all parts of the body, even the face, hands and joints, where there is apt to be some motion. After application of the solution, the pain produced by the burn is relieved. In erythematous areas, the patient has the sensation of a very cold application, and this sense of coolness persists even when the film is dry. As the solution is spread over denuded areas there is some stinging but this rapidly disappears. When the solution dries, it remains transparent, allowing one to detect immediately any evidence of infection beneath it. The fact that it is water soluble makes for great ease in its removal. Important, too, is the fact that it remains adherent to the denuded surface until complete epithelization has taken place. Where the solution together with the plastic film of polyvinyl chloride known as VinyLite was used we found that the dead tissue, even where full thickness of the skin was destroyed, separated from the underlying normal tissue between the sixteenth and twentieth day after the burn. The dead tissue appeared to be completely digested probably due to the action of the enzymes present in the exudate which collected beneath the film. This allows one to use a skin graft early before scar tissue has formed.

In several cases of severe burns in which the patients were admitted to the hospital sulfadiazine was given orally and adequate concentrations in the blood

thus maintained. We find that the proper way to administer the sulfonamide compounds when adequate concentration in the blood is desired is by controlled dosage given orally, or parenterally, with frequent determinations of their concentration in the blood.

In this series there were five deaths from burns. All patients had approximately 60 per cent or more of the body surface involved, most of which was deeply burned. The first, a woman aged 71, died from shock eighteen hours after admission. The second, a woman aged 59, who had also inhaled some of the fumes from the blaze, died from respiratory failure six days after admission. The postmortem examination in the latter case revealed bilateral partial pulmonary atelectasis and pleural effusion and moderate edema of the tracheal mucosa. The third patient, a man aged 38, who jumped five stories from a burning building, died twelve hours after admission, with a temperature of 107°. The primary cause of death was injury to the head. The fourth patient, a child aged 6 with 80 per cent of the body burned, the destruction extending through the full thickness of the skin, died three hours after admission from shock. The fifth, a woman with 60 per cent of the body surface involved by a burn extending through the full thickness of the skin, died from toxemia on the eleventh day after admission.

In this group of cases of burns we found that the combination of the casein solution and an already prepared film allows one to treat with ease the superficial as well as the deep burns. This bacteriostatic solution through its adhesive properties holds the film in place over the burn whether it is an erythema, a denuded surface or a total destruction of the skin. It also makes the film adherent to the normal skin about the burn, and in this manner the entrance of bacteria at the edge of the film is prevented. We feel that this offers a simple method for treating the burned patient, whether he is ambulatory or hospitalized. It eliminates the tremendous amount of nursing care attendant with sterile linen and the light cradle which we formerly used with the eschar type of treatment for the hospitalized patient and the time-consuming frequent dressings necessary with most of the local treatments used for the ambulatory patient. With our type of treatment the transparent film is removed if evidence of infection is seen beneath it or when one desires to debride the area for early skin grafting. In these last two instances the film is removed with ease since the casein solution which holds it in place is water soluble.

In our experience this method of treatment more readily controls the early local loss of plasma protein from the burned area than does petrolatum gauze or an ointment. It also eliminates the voluminous dressings necessary in the latter types of treatment to absorb this loss of fluid.

The solution when used with the films has also been found to be valuable in the treatment of abrasions and chronic ulcers and to support the skin incision, preventing the separation of the edges after removal of the sutures. The films have also been used to cover small deep skin grafts and the donor site.

Tissue which has been injured, regardless of the type of trauma, whether by a burn or in some other manner, is tissue whose physiologic status is uncertain. We know from tissue culture, as well as from *in vivo* studies that cellular metabolism and growth depend on the life of each individual cell whose nutrition comes from the surrounding extracellular fluid²⁰. All proteins are not equally effective in nutrition since each contains varying amounts of the amino acids. Only ten of

19 Footnote deleted by the authors

20 Willmer, E. N., *Tissue Culture*, London, Methuen & Co. Ltd., 1935

these, Rose²¹ believes, are essential for growth and its maintenance. Thus, by application of partially hydrolyzed casein in a water-soluble solution, we may be providing the best possible medium with which these injured cells of uncertain status can obtain the needed nitrogen for their growth and development. In the future the feeding of cells by local application of protein solutions may become as important a therapeutic measure as the parenteral administration of plasma and the amino acids. Use of hydrolyzed casein solutions in the treatment of diseases associated with protein deficiency was demonstrated by Elman²². In a like manner we have found it to be the most valuable substitute for plasma protein therapy in the local treatment of burns and wounds.

SUMMARY

A new solution containing casein is used in the local treatment of burns and wounds.

It is recommended that it be used with a flexible transparent film, several of which are described.

In this study there were 240 cases of burns and wounds which showed a low incidence of infection and a minimum of complications.

The *in vivo* and *in vitro* tests demonstrate that these casein preparations are nontoxic to tissue cells.

The method of treatment described allows one to utilize many of the fundamental principles of burn and wound therapy.

H. A. B. Dunning, Jr. helped in the preparation of the casein solutions used.

²¹ Rose, W. C. The Nutritive Significance of the Amino Acids, *Physiol Rev* **18** 109, 1938.

²² Elman, R. Parenteral Replacement of Protein with the Amino Acids of Hydrolyzed Casein, *Ann Surg* **112** 594, 1940.

PANCREATIC CALCULI

REPORT OF SEVEN CASES IN TWO OF WHICH CURE WAS
EFFECTED BY PANCREATICOLITHOTOMY

JOSEPH LIONELLO, MD

Associate Attending Surgeon, Kings County Hospital

BERNARD J FICARRA, MD

Resident Surgeon, Kings County Hospital

AND

NICHOLAS H RYAN, MD

Attending Surgeon, Kings County Hospital

BROOKLYN

The literature on pancreatic lithiasis reveals that investigators disagree on the exact number of cases reported. However, all are in unanimous agreement with the statement that this finding is rare. Various writers have attempted to establish the infrequency of pancreatic calculi. The figures obtained in our review of the literature are given in the accompanying table.

A study of these figures presents the possibility that reduplication occurs in some instances. It must also be conceded that many other cases are excluded which have not been reported. Haggard and Kirtley¹ reviewed the literature on pancreatic calculi in 1939. Their report covers a period of two hundred and seventy-one years. They could find authentic records of 204 cases. Only 65 of these were observed at operation. To this number should be added 3 reported by Townsend² and 18 seen at the Mayo Clinic³. This would bring the total number of reported cases to 225. King and his associates⁴ wrote of 4 cases of generalized calcification of the pancreas. His review of the literature revealed 11 other cases of calcinosis of the pancreas. Pilcher⁵ added 4 more cases of pancreatic calcinosis. These 19 cases of petrifying pancreatitis are not incorporated in the total 225 cases previously mentioned.

We are reporting 6 instances encountered at Kings County Hospital from January 1938 to April 1943, plus 1 case seen in private practice by one of us (J L). The diagnosis in 5 instances was by roentgenogram. Roentgenograms were taken on two or more occasions, so that there was no doubt of the diagnosis. Two patients were subjected to operation, and the diagnosis was confirmed at operation. Both of them were cured by surgical removal of the calculi.

ETIOLOGY AND PATHOLOGY

The exact cause of pancreatic calculi remains unknown. The dominant etiologic factor resides in stagnation of pancreatic juices as a result of chronic

From the surgical service of Dr Nicholas H Ryan

Read at the meeting of the Brooklyn Surgical Society on Oct 7, 1943

1 Haggard, W, and Kirtley, J. Pancreatic Calculi. A Review of Sixty-Five Operative and One Hundred and Thirty-Nine Nonoperative Cases, *Ann Surg* **109** 809 (May) 1939

2 Townsend, S R. Pancreatic Lithiasis, *Canad M A J* **43** 228 (Sept) 1940

3 Snell, A M, and Comfort, M W. The Incidence and Diagnosis of Pancreatic Lithiasis. Review of Eighteen Cases, *Am J Digest Dis* **8** 237 (July) 1941

4 King, A B, and Waghelstein, J M. Calcification of the Pancreas, *Arch Int Med* **69** 165 (Feb) 1942

5 Pilcher, J T. Personal communication to the authors.

inflammation with sclerosis Stagnation is allied to retention This is followed by a mild infection, with exfoliation of cells, precipitation of lime salts and formation of stones^c Some investigators maintain that the precipitating agent can be found in disease of the biliary tract^e

As is true of formation of stones elsewhere in the body, the chemistry of pancreatic calculi is not fully understood Two facts are prominent in the chemical account of the disease First, pancreatic stones are composed chiefly of calcium carbonate and tribasic calcium phosphate Second, normal pancreatic juice does not contain calcium in this form An inflammatory process in the pancreas, therefore, may be indicted for altering the chemical composition of pancreatic secretions This produces precipitation or deposition of calcium within the ducts³

Pathologically, pancreatic stones may be divided into true stones, found in the ducts, and false stones (calcification), found in the parenchyma True stones resemble salivary calculi They are usually smooth and rounded, rarely faceted Calculi vary in size, have a tendency toward multiplicity and often fuse to form

Cases of Pancreatic Lithiasis Recorded in the Literature

Author	Year	Cases Reported in the Literature	New Cases Reported by Authors
Sistrunk and Hartman cited by Mayo ^e	1921		4
Gross, O. and Guleke, N. <i>Die Erkrankungen des Pankreas</i> , Berlin, Julius Springer, 1924	1924	25	0
Hartman	1925		4
Schmieden V, and Sebening, W. <i>Arch f Klin Chir</i> 148 319 1927	1927		20
Ackman and Ross ⁹	1932	100	1
Bost ¹²	1935	107	2
Mayo ⁷	1936	125	17
Hoechstetter ^{12a}	1937	113	1
Haggard and Kirtley ¹	1939	204	2
Townsend ²	1937 1940	200	3
Snell and Comfort ⁸	1940		18
King and Waghelestein ⁴	1942	11 (diffuse calcification)	4 (diffuse calcification)
Pfleger ⁶	1943 (to be published)		4 (diffuse calcification)

branchings They are most often found in the pancreatic head, less frequently in the body and rarely in the tail⁸

A study of the pancreatic parenchyma in cases of calculi of the pancreas reveals definite pathologic changes Chronic interlobular pancreatitis has been described This gradually involves the entire gland with diffuse fibrosis The islets of Langerhans are last to be involved When extensive destruction of the islets occurs, the glycosuria of true diabetes results⁹

Further microscopic study shows progressive chronic pancreatitis with many areas of calcium deposits The arteries may show marked endarteritis Occasionally a subacute inflammatory process has been noted to involve not only the epithelial lining of the ducts but large areas of the gland tissue as well Rarely, acute or subacute pancreatitis with fat necrosis and peripancreatic induration is found³

6 Archibald, E W, and Kaufmann, M. *Surgical Diseases of the Pancreas*, in Lewis D. *Practice of Surgery*, edited by W Walters, Hagerstown Md, W F Prior Company, Inc, 1943, vol 8, chap 1

7 Mayo, T G. Pancreatic Calculi *Proc Staff Meet, Mayo Clin* 11 456 (July 15) 1936

8 Witherspoon J. Pancreatic Lithiasis, *South M J* 30 1064 (Nov) 1937

9 Ackman, I D and Ross A. Pancreatic Lithiasis *Surg, Gynec & Obst* 55 90 (July) 1932

Formation of cysts is not particularly uncommon. This occurs when the smaller pancreatic ducts become dilated. Abscesses in the parenchyma are seen occasionally. Among the late developments in the course of pancreatic lithiasis may be secondary fatty change in the liver. This depends on the disturbance in the secretion of the pancreatic hormone lipocain which has a regulatory function involving the deposition of fat in the hepatic parenchyma.¹⁰

Mention should be made of conditions found associated with pancreatic lithiasis. Among these are cirrhosis of the liver, cholelithiasis, cholecystitis, duodenal ulcer and atheroma of the splenic artery.¹¹

COMPOSITE CLINICAL PICTURE

There is no typical clinical picture. It is difficult to diagnose pancreatic calculi by the signs and symptoms. With the exception of roentgenologic studies, the laboratory offers little aid in diagnosis.

Epigastric pain is the most prominent symptom. This may be sudden or progressive. Radiation of the pain may occur transversely or to the left, rarely to the right. Often the pain simulates so-called indigestion or the colic of cholelithiasis or renal calculi. Extensive periods of freedom from pain are common. In some instances the pain is extremely severe. When the pain is associated with vomiting, acute pancreatitis is suspected. This is especially true when pancreatitis is concurrent.

Other aspects of the clinical picture may be loss of weight, diarrhea, sense of epigastric pressure or lowered blood pressure.

Glycosuria producing the picture of painful diabetes should suggest the possibility of pancreatic calculi. Fatty stools and jaundice have been reported as rare signs. Jaundice is caused by edema of the head of the pancreas or is due to obstruction of the lower end of the common duct by a calculus as it reaches the ampulla of Vater.¹²

In pancreatic lithiasis the clinical story is variable. It is dependent on the extent of pancreatic reflex digestive disturbances. To this may be added the effects produced on other abdominal organs by the destruction in the pancreas. Moreover, as is the case with stones elsewhere in the body, the condition may be almost entirely asymptomatic.³

THE DIAGNOSIS

The diagnosis is made by roentgenogram. The stones are radiopaque since they contain a large amount of calcium carbonate. Fluoroscopy does not reveal their location.

The position of the stones is usually across the upper part of the abdomen at the level of the second and third lumbar vertebrae. This allows them to be mistaken for gallstones, renal calculi or calcified retroperitoneal or mesenteric lymph nodes. There is no definite means of outlining the pancreas in the roentgenogram. However, it has been recognized that enlargement of the head of the pancreas by neoplasm, inflammation or cyst formation will result in distortion or spread of the duodenum.⁸

CASE REPORTS

We are presenting a report of 2 cases of pancreatic calculi. The first patient was operated on in 1940 at another hospital by one of us (J. L.). At that time

10 Faust, D. B. Pancreatic Lithiasis, *Ann Int Med* 9:625 (Nov.) 1935

11 Faust¹⁰ Townsend²

12 Bost, T. C. Pancreatic Lithiasis. Report of Cases, *Am J Surg* 29:85 (Jul.) 1935

two stones were removed from the head of the pancreas. The second patient was operated on at Kings County Hospital for the removal of four calculi in the tail of the pancreas. Both patients had uneventful recoveries. At the time of this writing they are enjoying good health.

CASE 1—A 56 year old clergyman entered the hospital on Aug 18, 1940. At that time his complaint was epigastric distress and pain. This pain did not radiate. Other symptoms were belching, intolerance to fatty foods and constipation. All these complaints were of three months' duration. The family history and the patient's past history were irrelevant.

On admission the temperature, the pulse rate and the respiratory rate were within normal limits. The blood pressure was 148 systolic and 80 diastolic. The patient was well built, somewhat adipose. A slight icteric tinge of the scleras was noted. The chest revealed nothing unusual. The abdomen was protuberant, no masses or organs were palpable. Tenderness was elicited on deep pressure over the right hypochondrium and epigastrium.

Laboratory studies demonstrated nothing unusual.

The impression was cholecystitis with cholelithiasis.

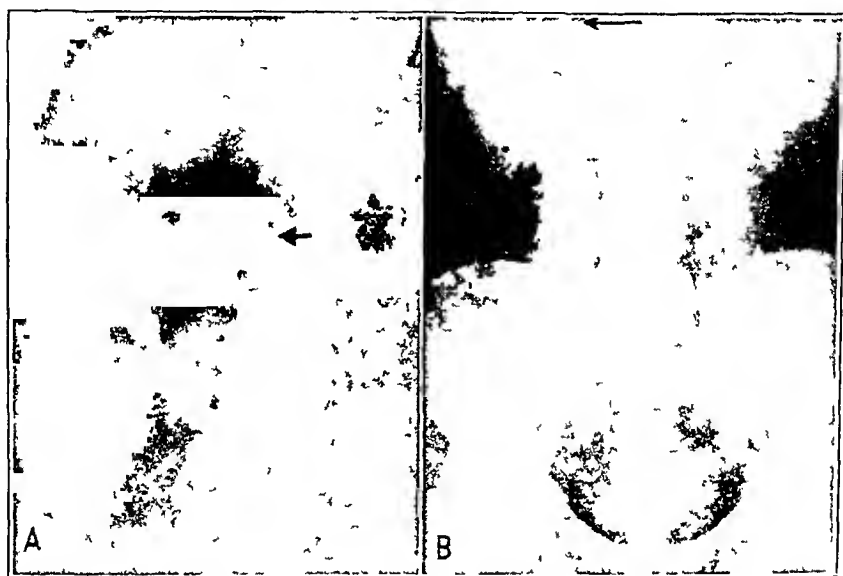


Fig 1 (case 1)—*A*, preoperative roentgenogram showing calculi in the pancreatic head. *B*, postoperative roentgenogram, taken thirty-one months after operation, showing absence of previous calculi. The small area of calcification was reported as not in the pancreas.

The day after admission cholecystography was performed. This revealed the gallbladder to be of small size. The dye concentration was below normal, indicating a moderate disturbance of biliary function.

A calcified mesenteric node near the level of the third lumbar vertebra to the left of the midline was reported. In addition, calcification at the level of the first lumbar vertebra, involving mesenteric nodes or possibly the pancreas, was seen.

On Aug 21, 1940, with the patient under spinal anesthesia, the peritoneal cavity was entered via an incision in the upper right rectus muscle. Exploration revealed the gallbladder to be slightly thickened, not inflamed and without calculi. The head of the pancreas was indurated. The pancreatic duct contained two calculi of about equal size, measuring $\frac{1}{4}$ by $\frac{1}{8}$ inch (0.64 by 0.32 cm). In the operative procedure the pylorus and duodenum were retracted, with exposure of the head of the pancreas. An incision was made into the pancreas. The calculi were removed with a clamp. The pancreatic incision was sutured with atraumatic catgut. The abdominal wall was closed in the routine fashion, with a drain in the operative site.

The postoperative course was uneventful. On one occasion urinalysis revealed a trace of sugar and a positive acetone reaction. No insulin was administered. Abdominal disten-

tion on the fourth day was combated with enemas. The drain was removed on the fifth postoperative day. The wound did not become infected, excoriation of the skin was prevented by application of a mixture of kaolin and olive oil.

The most recent postoperative roentgenogram of the abdomen was taken on May 27, 1943 (fig 1B). This revealed a single irregular calcific deposit in the right quadrant to the right of the twelfth vertebra. This may indicate that one calculus was not removed.

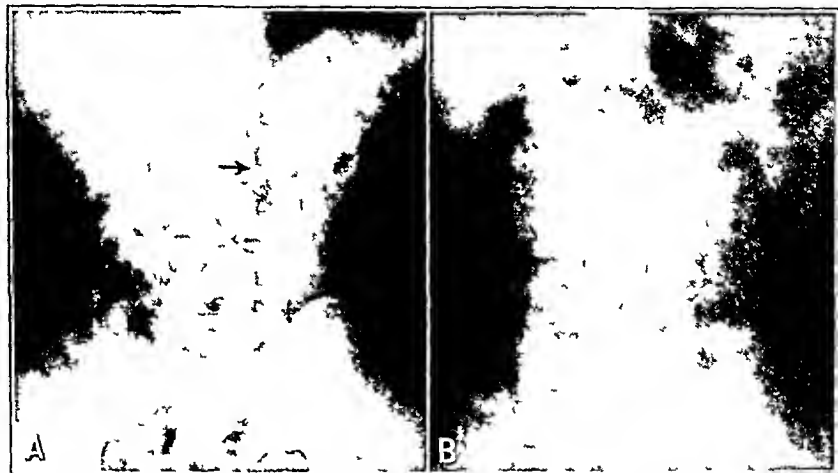


Fig 2 (case 2)—A, preoperative roentgenogram showing calculi in the tail of the pancreas. B, postoperative roentgenogram showing absence of previous calculi.

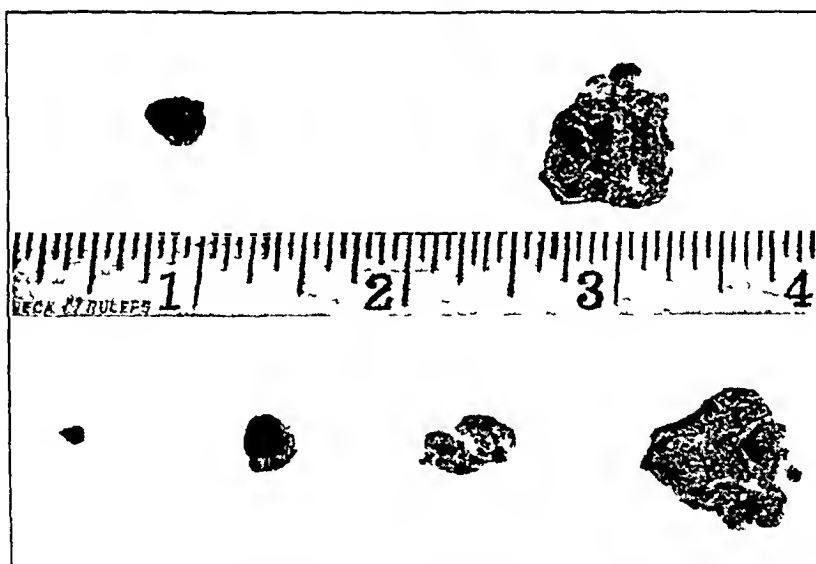


Fig 3—Photograph of calculi removed at operation (case 2)

The other calculi reported in the previous roentgenogram were not visualized in the recent study.

CASE 2—A 35 year old seaman of the merchant marine entered Kings County Hospital on March 21, 1942. His chief complaint was severe epigastric pain which commenced two days before admission. The pain was knifelike and intermittent in type. The asymptomatic periods were of several hours' duration. He had vomited on one occasion twenty-four hours before admission. He believed the vomitus contained clotted blood.

His past history included four operations on or about the stomach for gastric ulcer. It was not possible to secure adequate information on his previous surgical history, because he had been hospitalized in England and South Africa. As far as could be determined from the patient, the first operation occurred two years prior to his present hospitalization. At that time he underwent gastrorrhaphy for a perforated ulcer. The second operation was for postoperative adhesions. The exact nature of the third operation is not known. The fourth operation, gastroenterostomy, was performed two months before he entered Kings County Hospital.

The physical examination demonstrated nothing unusual. The patient was well developed and well nourished. The blood pressure was 114 systolic and 60 diastolic, the temperature, the pulse rate and the respiratory rate were within normal limits. The abdominal wall contained four longitudinal healed scars about one-half inch from each other in the midepigastrium. Tenderness was elicited in the epigastric region on slight pressure. There was tenderness of the costovertebral angles with spasm of the sacrospinalis muscles in the lumbar region.

The impression on admission of the patient was marginal ulcer or renal calculus.

Roentgenologic studies at Kings County Hospital revealed no intrinsic lesion of the stomach but a well functioning gastroenterostomy. A flat roentgenogram of the abdomen demonstrated a large calculus (about 2 cm in diameter) and a few smaller ones (a total of four) located inferiorly between the transverse processes to the left of the second lumbar vertebra. These calculi were believed to be in the pancreas. Intravenous pyelograms eliminated the possibility of their location in the kidney.

On April 13, 1943, with the patient under spinal anesthesia, the pancreas was approached through the gastrocolic omentum into the lesser peritoneal cavity. Four calculi were removed from the pancreatic parenchyma. These were located in the tail of the organ. The calculi were removed by incising the pancreatic tissue. A T tube was placed in the operative site and held in position with a purse string atraumatic suture. Closure of the abdomen was accomplished in the usual manner.

The salient feature of the postoperative course was a bloody fluid draining from the T tube for the first twenty-four hours, followed by a yellowish thick exudate for the next twenty-four hours. On the fourth day after the operation urinalysis showed sugar (1 plus) in the two specimens on that day. On the same day an increase in the amount of fluid draining from the T tube was noted. This drainage increased gradually until April 20, 1943, when the fluid assumed a yellow color and had the odor of fermented material. The skin was slightly excoriated at this time. Six days later the T tube was removed (twelfth postoperative day). The wound healed rapidly thereafter. Three weeks after the operation the patient was discharged. He has returned to the follow-up clinic every third week since leaving the hospital. Prior to his discharge from the surgical service, a flat roentgenogram of the abdomen proved that the calculi had been removed.

POSTOPERATIVE CARE

In the postoperative care of these patients we found that the wounds would heal in three weeks without difficulty and with little autodigestion of the skin. Excoriation was controlled with equal mixtures of kaolin and olive oil.

A low carbohydrate diet was given, partly to control the glycosuria and partly because this type of diet appeared to diminish pancreatic secretion.³ When the secretion appeared to increase, as demonstrated by the drainage, ephedrine sulfate, $\frac{3}{8}$ grain (24 mg) three times a day, was given. This reduced the output of the pancreatic juices by causing vasoconstriction. The foregoing practice is consistent with the known fact that the pancreas is sensitive to changes in the volume of blood flow.¹

SUMMARY AND CONCLUSIONS

It has been accepted in the past that pancreatic lithiasis is a rare entity. Perhaps it would be preferable to state that in clinical studies this condition is infrequently encountered, possibly because of the failure of the clinician to consider it in his differential diagnosis. The total number of cases, including those in this paper, we believe to be 232.

Pain is the most significant complaint. Associated diabetes or jaundice is seen rarely. The patient's story often suggests biliary or renal calculi. The

diagnosis is established by roentgenologic studies of the abdomen. A simple flat roentgenogram of the abdomen will reveal the calculi.

When a diagnosis of pancreatic lithiasis is made surgical intervention is indicated. The safest approach to the pancreas is through the gastrocolic omentum according to American authors. Where this approach has been utilized there is reported an operative mortality of 7 per cent.¹³ Palliative treatment is of little avail. Unless the calculi are removed the patient with symptoms must continue to complain of discomfort and look forward to the possibility of gradual destruction of the pancreas.

217 Clinton Avenue
1702 Forty-Sixth Street
142 Jeromeon Street.

13 (a) Hoechstetter S. Pancreatic Lithiasis. Report of a Case. *Am J Roentgenol*
37:35 (Jan) 1937. (b) Boston.

SIMPLIFIED SURGICAL APPROACH TO THE HIP

ROSS SUTHERLAND, MD, AND M JOHN ROWE JR, MD

LOS ANGELES

LONG BEACH, CALIF

Many approaches to the hip joint have been described. All have advantages and disadvantages. It is safe to say that at the present time the Smith-Peterson approach is used most widely by American orthopedic surgeons. This approach appears to give a maximum visualization of the hip joint with a minimum of operative trauma.

However, some disadvantages of the approach are inevitably apparent. There is often adherence of the scar to the iliac crest. Weakness of the gluteal muscles, particularly of the abductor and internal rotator muscles, is always present to some degree because of the reflection of the gluteal origins from the iliac surface. Hemorrhage is at times formidable with the section of muscles and tendons necessary to open the field. Institution of mobility of the joint is always delayed because of the necessity of allowing healing of the replaced soft tissues.

With the recent use of metal fixatives to replace bone attachments of muscles and allow early function during the healing of the bone, it is evident that further simplification of this standard surgical procedure may be accomplished, with resultant decrease in some of the disadvantages mentioned.

The technic adopted is founded on the principle that functional return is more rapid when muscle attachments are removed with a portion of the bone and the bone is replaced with internal fixatives. The principle is the same in that the Sartorius group is removed intact with the anterior superior iliac spine, the rectus femoris with the anterior inferior iliac spine and the gluteal group with its insertion into the trochanter of the femur rather than by elevation of the origins from the iliac wall. Such technic allows the reflection of the muscles in planes with a minimum of hemorrhage from intramuscular vessels. After conclusion of the operation the bone portions with attached muscles are replaced in the reverse order with metal fixatives and often the trochanter is transplanted distally to allow greater abductor function with a longer lever arm. Motion may be instituted within the first two weeks and may be active because of the firm fixation of the muscle attachments.

REPORT OF CASES

CASE 1—D N, a girl aged 12, had ankylosis of right hip following infectious arthritis. There severe flexion and adduction deformity with compensatory scoliosis. On May 5, 1943 reconstruction of hip joint was performed by use of the approach described. The superior and inferior anterior spines were removed with the osteotome and reft with their attached muscle groups. The trochanter osteotomized and reflected with the gluteal group. Capsule of the hip was then opened, with complete exposure of the femoral head and acetabulum. Ankylosis was severed and the hip dislocated so that the entire irregular overgrown margin of the femoral head could be excised leaving only a small area of cartilage in the region of the ligamentum teres. Acetabulum was then somewhat shallow and a metal shelf was applied to its upper margin to provide luxation of the hip. The femoral head was retracted, the capsule closed and the trochanter transplanted distally and fastened with two vitallium nails. The anterior iliac spine was replaced with one nail and the superior iliac spine with a second nail. The fascia and skin closed, and no external fixation or traction was used. The patient's condition remained almost unaltered throughout the operation, which was performed in less than an hour. A transfusion, together with pain administration of fluids, was given during the operation, as has been customary, but it was felt that this unnecessary because of the lack of hemorrhage. Convalescence was rapid and uneventful. Pool therapy begun three weeks after operation, on discharge from the hospital.

CASE 2—H R, a woman aged 39, had congenital dislocation of the left hip with secondary ankylosis, changes and pain. After a preliminary exercise program reconstruction of the hip with application of a metal shelf was performed on May 19, 1943. Traction was applied by the Russell method for ten days after operation, and motion of the hip was begun in traction ten days after operation. The patient was allowed the use of crutches immediately after removal of the traction. She began swimming three weeks after operation and full weight bearing at four weeks. Discomfort comparable to that with the usual operative procedure was avoided.

A simplification of the surgical approach to the hip joint is presented which decreases surgical shock and allows early function of the joint by utilization of internal metal fixation of the bone attachments of muscles which must be reflected to expose the joint area.

1660 Terminal, Long Beach

501 Professional Building Long Beach

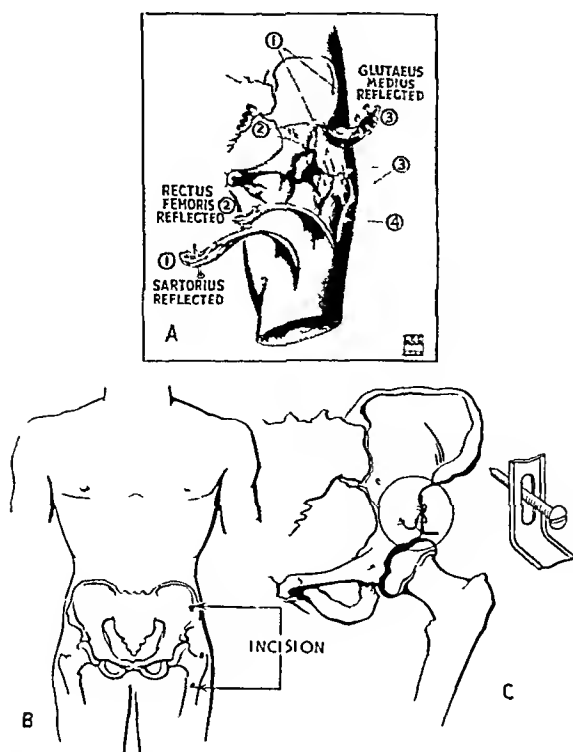


Fig 1—*A*, surgical approach to hip 1, reflected anterior superior iliac spine, 2, anterior inferior iliac spine, 3, trochanter of femur, 4, site of distal transplantation of trochanter *B*, incision in skin shown in dotted line on small figure *C*, site of attachment of metal hip shelf when used shown in second small diagram



Fig 2 (case 1)—*A*, fibrous ankylosis of hip from infectious arthritis *B*, postoperative roentgenogram showing metal fixatives and shelf

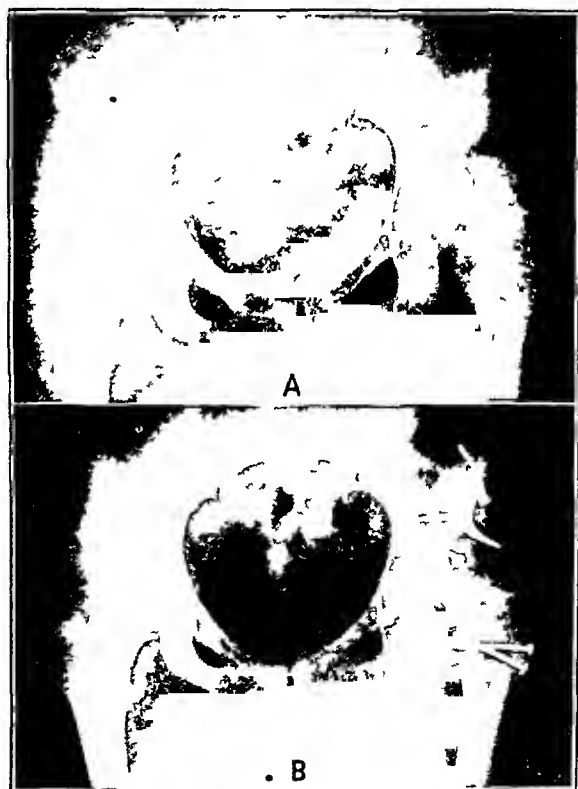


Fig 3 (case 2)—*A*, congenital dislocation of hip with painful arthritis in false acetabulum *B*, postoperative roentgenogram showing trochanter transplanted distally

REVIEW OF UROLOGIC SURGERY

ALBERT J SCHOLL, M D
LOS ANGELES

FRANK HINMAN, M D
SAN FRANCISCO

ALEXANDER VON LICHTENBERG, M D
MEXICO, MEXICO

ALEXANDER B HEPLER, M D
SEATTLE

ROBERT GUTIERREZ, M D
NEW YORK

LIEUTENANT COMMANDER GERSHOM J THOMPSON (MC), USNR*

EDWARD N COOK, M D
ROCHESTER, MINN

EGON WILDBOLZ, M D
BERNE, SWITZERLAND
AND

VINCENT J O'CONOR, M D
CHICAGO

(Continued from page 88)

PROSTATE

Prostatectomy Versus Transurethral Resection—Young³¹ discusses the question of perineal prostatectomy versus transurethral resection of hypertrophy and cancer of the prostate. He states that there are in the records of the Brady Urological Institute hundreds of case histories which testify to the relief of obstruction, frequency, difficulty, pain and other symptoms presented by patients who have been successfully treated by transurethral prostatic resection either with his cold-cutting punch or one of its modifications or with the electric resectoscope of McCarthy. He reports a series of patients who complained of unsatisfactory results after one or more transurethral resections elsewhere.

He first describes those cases in which prostatic lobes had been left behind or developed after transurethral resection, removal of which by perineal prostatectomy afforded relief of the symptoms of which the patient complained. In some of these cases the transurethral operations had been manifestly inadequate. Often only the middle lobe was thoroughly resected and the lateral lobes were incompletely removed. In many instances, however, the patients had obtained relief of obstruction for a time, but the remaining portions of the hypertrophied lobes continued to grow and ultimately produced obstruction to urination and other distressing symptoms.

In other cases these symptoms were greatly aggravated by the presence of infection, not only of the bladder and urethra, but of the remaining prostatic tissue. Chronic prostatitis appeared to be a frequent sequel of transurethral resection, and in most instances resisted all efforts at sterilization by modern chemotherapy including the various sulfonamide compounds.

* The opinions and assertions contained herein are the private ones of the various writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

³¹ Young H H. Perineal Prostatectomy Versus Transurethral Resection for Hypertrophy and Cancer of the Prostate. Surg., Gynec. & Obst. 77 1-15 (July) 1943.

In some cases in which no residual urine was found the irritation was sufficient to produce frequent micturition and even dysuria. In such cases a second and even a third transurethral resection had failed to do away with the distressing symptoms which followed the first resection.

In a few cases vesical calculi were present, having recurred in 1 case after a second resection and removal of the stones. In some cases calculi in the tissue of the prostate gland itself were responsible for discomfort and the persistence of pyuria and infection. Perineal prostatectomy, by affording an opportunity to remove completely the stone-bearing prostatic tissue, finally gave complete relief.

A number of these patients had not been relieved by a second transurethral resection elsewhere but were promptly cured by enucleation of the obstructing infected lobes through the perineum.

These cases seem to prove conclusively that in prostates of considerable size, and even in some of moderate size, enucleating prostatectomy is a far more scientific procedure than chipping away the periurethral prostate bit by bit, and rarely removing all the adenomatous lobes completely.

But it is in the carcinomatous prostate that the routine use of transurethral resection in all cases in which there is prostatism has its most dire results. In most of the cases of cancer reported by Young a considerable period had elapsed between the transurethral resection and the time that the patient was seen, with cancer of the prostate too advanced for the radical operation. In these cases the histories frequently disclosed that the patients had been treated for months before being subjected to a transurethral operation.

Young concludes, from this study of the 200 patients who were subjected to one or more transurethral resections before coming to him, that for many cases, particularly those in which the prostates are considerably enlarged, complete enucleation of the hypertrophied lobes through the perineum gives better results and is no more dangerous than transurethral resection.

Prostatitis and painful urination are certainly less common after perineal prostatectomy than after transurethral resection. Another great advantage of the perineal procedure is the opportunity which it affords to make a diagnosis and effect a cure of carcinoma of the prostate.

Undoubtedly many conditions, particularly bars, contractures and small hypertrophies, can be dealt with efficiently by transurethral resection. But in the cases of larger hypertrophies, those in which there are calculi in the prostate and those of chronic prostatitis, Young's study of 200 cases shows that perineal prostatectomy is distinctly superior to transurethral resection.

Prostatism is so complex in its symptoms and so varied in its pathologic changes that it can be handled satisfactorily only by careful selection of the operative procedure best suited to obtain a radical cure.

The exclusive use of transurethral resection for all types of prostatic obstruction even the very large and the malignant, is indefensible.

Griffin³² states that mortality and morbidity rates for transurethral resection are high for the nation as a whole. In resection centers and in the practice of individual experts they are low. The misconception by physicians, hospital staffs and patients that this operation is a simple procedure does much to maintain unfavorable national statistics. Griffin gives a summary of results in his first 83 cases. He considers the mortality rate of 11 per cent in this series as indicative of what can be accomplished in new surroundings after accredited training in transurethral prostatic resection.

³² Griffin, M. The Resectionist Considers the Case Against Transurethral Prostatic Resection, *J Urol* 49: 452-456 (March) 1943.

Recurrent Symptoms—Cook³³ discusses the causes and treatment of symptoms recurring after transurethral prostatectomy. He states that transurethral prostatic resection has almost completely supplanted other forms of prostatectomy at the Mayo Clinic.

The narrowing of the urinary stream is due in many cases to inadequate removal of tissue. The narrowing may have been present preoperatively or it may result from trauma to the urethra at the time of operation. The latter can be avoided by gentle and satisfactory dilation of the urethra before the small resectoscope is inserted. If this is not possible, perineal urethrotomy should be performed and the instrument passed through this opening. If a stricture and associated periurethritis do develop postoperatively, the passage of a sound frequently will relieve the patient's distress. Many times a narrowed stream occurs because of constriction just back of the meatus in the fossa navicularis. For this type of stricture dilation is of benefit.

The danger of massive bleeding is almost entirely gone in fourteen days, and after this time, if bleeding does occur, it is not likely to be serious. With the slough incidental to the normal healing process, bleeding occasionally will occur. This usually can be controlled satisfactorily by lavage of the bladder. If this procedure is not sufficient, an indwelling catheter left in place for twenty-four to forty-eight hours will control the bleeding. Inadequate removal of tissue may be responsible for continued hemorrhage. Whenever continued hemorrhage occurs, cystoscopic examination is indicated. Many times an occasional few drops of blood in the urine can be controlled satisfactorily by the administration of 1 grain (0.065 Gm.) of methylthionine chloride U. S. P. (methylene blue) three times a day. This has undoubtedly some hemostatic properties, but a contributing benefit for the anxious patient is the fact that it disguises the presence of bleeding.

Incontinence is a rare complication, and in cases of benign hyperplasia of the prostate is almost always due to faulty technic of the surgeon. In a small group of cases trauma to the sphincter, the result of evulsion of the fibers rather than actual cutting of the sphincter, is the cause. In such instances the incontinence eventually disappears, and its disappearance can be helped by instructing patients to exercise the muscles of the perineum by regular voluntary contractions. Urinary leakage is frequently seen after operations for malignant lesions because of destruction of the sphincteric action by actual invasion of the control muscle by the tumor. When this occurs, a penile clamp is most helpful.

Inadequate removal of tissue is the usual cause of residual urine. Because of failure to remove sufficient tissue, infection undoubtedly will continue and the patient sooner or later will fall heir again to his original symptoms of obstruction. Infection may cause residual urine and if present, should be eradicated. If residual urine is noticed immediately after operation, diverticulum or atonicity of the bladder may be the cause. During the last few years a large group of patients who have had large diverticula of the bladder have undergone transurethral resection at the Mayo Clinic. In almost all cases the diverticulum has not required any further surgical treatment and has eventually shrunk to an imperceptible lesion if the tissue at the vesical neck was adequately resected. In some instances, daily catheterization has been needed postoperatively for varying periods in order to enhance the shrinking. Such catheterization also should be resorted to in the atonic bladder incidental to obstruction of long standing in which the amount of residual urine is large. Eventually vesical tone will be restored by this procedure.

33 Cook, F. N. Causes and Treatment of Symptoms Recurring After Transurethral Prostatectomy. Proc. Staff Meet., Mayo Clin. 18:156-159 (May 19) 1943.

Infection is most commonly a cause of dysuria. Immediately after operation there is not much reason for attempting to eradicate existing infection. If it is great, however, lavage of the bladder and chemotherapy by mouth may serve to reduce the amount, but complete sterilization of the urine can rarely be obtained. Cook feels that no real effort to eradicate infection should be attempted for four to six weeks after operation. A word of caution should be interjected concerning the use of sulfonamide compounds for older patients. Small doses, never exceeding 45 grains (3 Gm.) daily for a period of one week, will usually suffice.

The intake of fluid is often responsible for frequency and nocturia. For some reason patients feel that a large intake of fluid will improve their stream. They should be instructed to drink 8 glasses (2 liters) of fluid daily and to do most of this before 4 p. m. The observation also has been made that older persons put out more urine at night than young persons. The cause of this is uncertain, but it probably is related to the fact that at rest in bed their circulation is improved, and with a greater amount of blood passing through the kidneys urinary secretion is increased. Nocturia of the aged frequently occurs, and the only possible help is obtained by reduction of the intake of fluid late in the day.

Sexual disturbances are not common and come without any degree of regularity. Usually there is no change of libido or potentia, but in some cases these are increased and in others decreased. The most frequent complaint is the loss of ability to ejaculate. This is the result of anatomic factors. As the region of the vesical neck is opened widely at the time of operation, it is easier for the ejaculated semen to pass into the bladder than out through the urethra. A few words of reassurance are again all that is necessary to help the patient and put his mind at ease.

Epididymitis may occur but can usually be avoided if the patient is instructed not to let his bladder get too full, not to strain and not to do any heavy work for three or four weeks after operation. When epididymitis does develop, adequate support to the scrotum, rest, warm sitz baths and chemotherapy usually will clear up the condition.

Prostatic abscesses are rare. Thrombophlebitis of the veins of the legs may occur and, if it does appear, it should be treated as usual. Rest, elevation of the extremity and application of hot moist packs are indicated. This complication may be followed by fragmentation of the clot with secondary emboli reaching the lung and producing infarction, in rare cases death ensues.

Prostatic Obstruction and Diverticula—Adams³⁴ presents 26 cases of diverticula of the bladder occurring in a series of 200 consecutive cases of prostatic obstruction. Twenty-four patients were treated successfully by so-called conservative measures without diverticulectomy, although 3 patients are considered only improved and 1 was not followed, the remaining 20 patients are considered cured. Indications for diverticulectomy occurred in only 2 of the 26 cases, and the general indications for occasional primary or secondary diverticulectomy are given. Most patients suffering from prostatic obstruction with associated diverticula can be successfully treated by removal of the obstruction at the vesical outlet. Manual dilatation or transurethral resection of the orifice of the diverticulum occasionally is thought indicated and of some slight value in promoting better drainage.

Cancer—Dean, Woodard and Twombly³⁵ state that from the clinical viewpoint the observations suggest that patients who have cancer of the prostate are made

34 Adams, P. Prostatic Obstruction Complicated by Diverticula of the Bladder, *J Urol* 49 558-571 (April) 1943.

35 Dean, A. L., Woodard, H. Q., and Twombly, G. H. The Endocrine Treatment of Cancers of the Prostate, *J Urol* 49 108-117 (Jan.) 1943.

more comfortable when treated by surgical castration or by the administration of estrogens than when treated by other methods and perhaps live longer. The majority, however, after a variable period of improvement relapse and die of the disease. It may be that endocrine treatment exerts different degrees of benefit on different types of prostatic cancers to such a degree as to provide even a cure in an especially fortunate type. It will be remembered that prostatic cancers may vary considerably in their natural history and in their response to other forms of treatment, such as irradiation. Although an attempt has been made to distinguish clinical types by their response to endocrine treatment, this has been unsuccessful as yet, possibly because too few patients have been observed.

In their experience, the clinical benefit which follows the oral administration of diethylstilbestrol is as great as that which follows surgical castration.

From the research viewpoint it seems well demonstrated that the natural history of cancers of the prostate may be definitely modified by changes in the endocrines. These changes can be produced by such measures as surgical castration or the administration of estrogens. It is possible that, from this starting point, not only the cure but also the prevention of prostatic cancers can be brought about by the clinician working in collaboration with the biochemist.

Prostatitis—Howard³⁶ states that the word "prostatectomy" is a misnomer. The compressed residual of the prostate after removal of the adenomatous portion by so-called prostatectomy differs histologically only in the diminished number of gland units, which are as vulnerable to infection as those of the unaltered gland. In addition to the common pyogenic bacteria which usually are present in prostatitis, certain inflammatory conditions of the prostate can be explained only on the basis of a virus infection. Howard presents 3 cases of prostatitis subsequent to prostatectomy.

URETHRA

Periurethral Extravasation—Steller³⁷ discusses urinary infiltration in relation to periurethral fascia. He distinguishes three different layers of fascia and states that the superficial or Colles' fascia does not necessarily correspond to that referred to by Wesson, who described a continuous fascial layer completely covering the penis and scrotum. Steller states that Colles' fascia is composed of portions from superficial abdominal fascia, the cremasteric fascia, the penile fascia and the superficial fascia of the perineum. The scrotum does not have any fascial layers corresponding to this complex fascial group. This is important in regard to the localization and spread of urinary infiltration, which usually is due to an inflammatory process. The second layer of fascia consists of the aponeurosis of the abdominal oblique muscles, the suspensory ligament of the penis, the external layer of the periosteum of the os pubis and the external sheet of the urogenital diaphragm. The third fascial group is composed of the fascia from the transverse abdominal muscles, the internal periosteum of the os pubis and the internal sheet of the urogenital diaphragm.

The second part of Steller's paper deals with the pathologic factors leading up to urinary infiltration. In most cases there is an injury to the mucosa of the urethra either by mechanical or by bacterial trauma. In 90 per cent of the cases, stricture of the urethra was present, usually distal from the point of lesion. In 75 per cent there was a history of gonorrheal infection. The urinary extravasation

36 Howard H W. Prostatitis Subsequent to Prostatectomy. *J Urol* 49:450-451 (March) 1943.

37 Steller L. Die periurethrale Ummfiltration und die periurethralen Faszien, *Ztschr f Urol* 35:192-204 1941.

may be spread in three different ways, which differ greatly from each other as to their prognosis. In one the infection starts at the bulbous urethra and spreads between the superficial fascia and the skin. Next, there is an infiltration of the perineum, scrotum and inguinal and pubic regions. The prognosis for life is good. In the second type, the infection occurs in the membranous urethra and spreads between the two sheets of the urogenital diaphragm. After several days the diaphragm may rupture either outward, in which case the prognosis is good, or inward into the organs of the pelvis, in which case the prognosis is bad. In the third type, the infection starts in the prostatic urethra, infiltrates all the organs of the pelvis and in most cases causes death.

The treatment in all types is incision of the infiltrated region down to normal tissue and drainage of the bladder. It is necessary to do both, neither is sufficient without the other.

Urethral Caruncle—McKim, Smith and Rush³⁸ state that every female patient who has symptoms of frequency and burning is a possible victim of a urethral caruncle. In 95 per cent of their series of 202 cases the caruncle was intraurethral, behind a tight meatus. In 99.7 per cent it was located on the lower surface of the mucous membrane at the urinary meatus. The lesion is more frequent between the ages of 50 and 60 years than in other age periods. Every caruncle should be regarded as requiring surgical treatment, the choice of the surgical technic is dependent on the type, size and location of the growth. McKim, Smith and Rush prefer radical removal, followed by local treatment with the high frequency current if indicated. In this series no malignant lesions were found.

Diverticulum—Fagerstrom³⁹ states that 'diverticula of the anterior urethra result from obstructive lesions, from lesions that damage the urethral wall or from a combination of the two. A small group remains which cannot be explained by such conventional factors. An attempt has been made to establish a rational cause for this group. A possible solution was afforded by the fact that in the cases presented by Fagerstrom the diverticula developed in men who had lost urinary control after prostatectomy. If the prostate and the spongy urethra are supplied by a common innervation, as seems likely, and these nerve pathways are subject to injury, either by pressure necrosis from a prostatic tumor or by actual surgical trauma, then formation of diverticula and incontinence become but two phases of a single neurogenic dysfunction. The cause of incontinence following prostatectomy is a practical problem and is far reaching in its implications.

URINARY INFECTION

Pyuria—Florman and Bass⁴⁰ discuss pyuria of the newborn treated with sulfathiazole and report 3 cases of pyuria occurring in newborn boys. In 1 the pyuria was associated with uremia and failure to gain weight and in 1 with jaundice and *Escherichia coli* sepsis and in the third it was probably secondary to an infected circumcision. All the boys were treated with sulfathiazole and recovered. The drug seemed to accelerate their recovery. The physiologic changes taking place in

38 McKim, G. F., Smith, P. G., and Rush, T. W. Urethral Caruncle, *J. Urol.* **49** 187-191 (Jan.) 1943.

39 Fagerstrom, D. P. Etiology of Acquired Diverticula of the Anterior Urethra and Its Relation to the Cause of Post-Prostatectomy Incontinence. Report of Two Cases, *J. Urol.* **49** 357-369 (March) 1943.

40 Florman, A., and Bass, M. H. Pyuria of the Newborn Treated with Sulfathiazole. A Report of Three Cases Illustrating Different Aspects of the Syndrome. *J. A. M. A.* **122** 656-658 (July 3) 1943.

the neonatal period appeared to be conducive to the development of infection of the urinary tract in this age group

Sterile Pyuria—Moore⁴¹ reports a study of 80 cases of sterile pyuria. On an etiologic basis they can be divided into three main groups

1 Noninfective	
Urinary calculi	20
Toxic disease (nephritis)	9
2 Infective (organisms demonstrable on microscopic examination of the centrifuged urinary deposit)	
Resolving infections of the urinary tract	2
Faulty technic	4
Urinary tuberculosis	24
3 Infective (no organisms demonstrable on microscopic examination of the centrifuged urinary deposit)	
Resolving infections of the urinary tract	9
Carcinoma of the bladder	2
Prostatitis	5
True infective abacterial pyuria	5
(These 5 cases presented in detail)	
Total	80

The literature contains a few references to abacterial pyuria. Faltin in 1909 was the first to draw attention to cases of sterile pyuria in which tuberculosis could be excluded. Kretschmer in 1921 reported 200 cases of pyelitis. In 21 of these the urine contained pus but was sterile on culture. Wildbolz stressed the resistance of the disease to ordinary forms of treatment and its miraculous cure by the intravenous injection of an organic arsenical preparation. From this time the disease has been more widely known.

At present no definite cause can be assigned to true infective abacterial pyuria. The few cases which have been reported have led various authors to give their own ideas of the cause. The possibilities can be considered under the following headings: (1) bacteria, (2) toxins, (3) syphilis, (4) fungus and (5) virus.

There is no evidence of the method of infection of the urinary tract. This may be hematogenous, lymphogenous or ascending from the lower part of the urinary tract. As different parts of the urinary tract bear the brunt of the infection in different cases, it is probable that the organism reaches the urinary system through the blood stream.

The disease is most common in young male adults. It is by no means confined to these, however, as in the 5 cases here analyzed only 1 patient was a very young person, and 3 were females. The onset may be acute or gradual. Symptoms of cystitis then present themselves and consist of great frequency of micturition, dysuria and sometimes hematuria. When the bladder and posterior urethra are the main sites of infection, there are terminal urethral pain and terminal hematuria.

On clinical examination no physical signs are found. Detailed examination shows that the urine contains many pus cells but no organisms on microscopic examination and culture. When the upper part of the urinary tract is affected tests of renal function may show slightly diminished function on the affected side. Intravenous urograms show some dilatation of the pelvis and ureters on the affected side and in some cases small filling defects due to follicular pyelitis and ureteritis. Cystoscopy shows nonspecific inflammatory changes in the bladder which are not

⁴¹ Moore T. Sterile Pyuria with Special Reference to True Infective Abacterial Pyuria. *J. Urol.* 49:203-223 (Feb.) 1943.

particularly marked around the ureteral orifices. There are none of the characteristic appearances of urinary tuberculosis.

The disease is most likely to be diagnosed as urinary tuberculosis. In true abacterial pyuria tubercle bacilli are never found in the urine by any method of investigation. The clinical picture is different in that a patient who has urinary tuberculosis eventually will have general constitutional disturbances and loss of weight. Intravenous urograms made when the disease is in an advanced stage will show erosion of the calices and destruction of the renal parenchyma. The cystoscopic picture is quite different. Urinary tuberculosis must never be diagnosed unless bacilli are observed in the urine. With modern methods of investigation this is possible in all cases of active tuberculosis.

Another disease difficult to distinguish from true infective abacterial pyuria is subacute prostatitis. In this disease pus may be present in the urine, but no organisms may be found. Culture of the prostatic secretion will reveal an organism in all cases if the methods detailed in this thesis are carried out.

If the disease is not recognized the course is prolonged. The capacity of the bladder becomes progressively reduced, and the patient is left in the same miserable state as one suffering from urinary tuberculosis.

In true infective abacterial pyuria when a correct diagnosis is made and treatment with neosarsphenamine is instituted the prognosis is excellent.

The disease is resistant to all forms of therapy except that which is specific for it. Occasionally the symptoms are relieved by lavage of the bladder, but eventually they reappear and can be completely cured only by intravenous injections of neosarsphenamine.

Wildbolz was the first to point out the excellent results of treatment of true infective abacterial pyuria with neosarsphenamine. This therapy is entirely empiric but the results are truly remarkable. In no other disease are they so constant or so rapid. The treatment is so specific that it may be used as an accurate therapeutic test. It is important that a small dose be given. It should be withheld from patients who have deficient hepatic or renal function.

Tuberculous Bacilluria—Albuquerque, Campos da Paz and Fontes Magarao⁴² offer a contribution to the study of tuberculous bacilluria. Their investigation was carried out on patients who had chronic, extensive and progressive pulmonary tuberculosis, with acid-fast bacilli demonstrable in the sputum. This type of patient was chosen as offering the greatest possibility of bacillemia. The patients were followed until death.

Because the presence of tubercle bacilli in the blood stream is always transitory and hard to detect, an endeavor was made to detect bacilluria by means of daily examination of the urine for tubercle bacilli. Such examinations were continued over periods of weeks and sometimes months, until death. The sediment of the twenty-four hour specimens was examined microscopically, cultures were made and guinea pigs were inoculated.

When the patient died the entire genitourinary tract was thoroughly examined. If a positive bacteriologic finding was not in accord with the results of this pathologic examination, serial sections were made of the kidneys, including the pyramids and the papillae. A total of 30 patients were observed. Twenty-three died and a pathologic examination of their genitourinary tracts was made. An analysis of the findings for the 23 patients who died showed that 5 had tuberculous lesions of the genitourinary tract, with tubercle bacilli in the urine. Three had

⁴² Albuquerque, P. F., Campos da Paz, Jr. and Fontes Magarao. A Contribution to the Study of Tuberculous Bacilluria, *J. Urol.* 49: 590-594 (April) 1943.

tuberculous lesions of the genitourinary tract without demonstration of the organisms in the urine. In 12 cases the results were totally negative. In 4 other cases the bacteriologic examination of the urine revealed typical colonies of tubercle bacilli by culture and the organisms were pathogenic for guinea pigs, but serial sections of the patients' renal pyramids and papillae and examination of other regions of the genitourinary tract did not disclose the presence of any tuberculous lesions.

Albuquerque, Campos da Paz and Fontes Magarao conclude that among patients in the terminal stages of chronic pulmonary tuberculosis there may be an elimination of tubercle bacilli through the kidneys while no tuberculous lesions are demonstrable in the genitourinary system.

ANURIA

Kasten⁴³ states that anuria is a symptom of a shocklike syndrome rather than a clinical entity. The filtration-absorption theory of renal function leads to clearer understanding of causes of anuria, and to more effective means of prevention and treatment. In the majority of cases in which anuria is a symptom, a marked fall of blood pressure is a constant feature. An outline of the causes of anuria is presented in which the grouping of the many and various factors is made on a physiopathologic basis.

The active treatment of circuloexcretory anuria consists largely of measures to restore adequate blood volume and blood pressure. The use of vasoconstrictors, natural and synthetic preparations of adrenal cortex, transfusions of blood and blood plasma and renal decapsulation is discussed. The hazards in the use of some of the sulfonamide compounds and of incompatible blood in transfusion have been stressed. These types of intrarenal obstruction should rarely occur in properly supervised medical and surgical management. In cases of obstructive anuria the overcoming of the obstruction frequently is in itself not enough, but all the measures as outlined for the treatment of circuloexcretory anuria may need to be employed if the patient is to be given the best chance for recovery.

A brief analysis of 9 cases is presented in which anuria and low blood pressure were prominent symptoms in a shocklike syndrome. There were 4 deaths and 5 recoveries. The patients who recovered did so largely because they had the benefit of a better understanding of the underlying causative factors together with the use of more effective therapeutic agents.

Hamer and Mertz⁴⁴ report 22 cases of anuria. In 4 of these anuria followed surgical operations, in 2 it followed acute infection of the respiratory tract, in 2 it was due to poisoning by mercury bichloride. In 4, it followed medication as follows: a sulfonamide compound, 2, bismuth, 1, and arsphenamine, 1.

In 8 cases anuria was due to urinary calculus: in 5, to stones in (surgical) solitary kidneys, in 2, to bilateral renal calculus and in 1, to unilateral renal calculus. One occurred in leukemia and 1 in cardiac decompensation due to mitral stenosis.

Three of the 4 patients who had anuria after surgical operations died, as did also the 1 whose anuria was due to leukemia, the 2 whose anuria was due to acute infection of the respiratory tract and the 2 who were poisoned with mercury bichloride. All of these belong in the classification of patients with renal anuria.

Of the 8 patients with anuria due to urinary calculus, only 1 died.

43 Kasten, H. F. The Etiology of Anuria with Emphasis on Prevention and Treatment. An Analysis of Nine Cases. *J. Urol.* **49**: 93-107 (Jan.) 1943.

44 Hamer, H. G. and Mertz, H. O. Anuria, *Trans Am A Genito-Urin Surg Soc.* **35**: 153-173 1942.

In discussing Hamer and Mertz's article on anuria, McClelland⁴⁵ makes special reference to crush injuries. In England at the present time, many people are being crushed under the bricks and mortar and stone buildings that are being knocked down by bombing. In such cases a considerable region of contusion in the muscles develops, along with some fractures. These regions of contusion are said to give off some sort of toxin that within twelve hours produces complete anuria. The patient will be fairly well for a period of six or seven days and then will die suddenly. During that time, there are the usual signs of anuria, the nonprotein nitrogen increases, slight edema comes on, and then suddenly on the sixth or seventh day the patient dies. When necropsy is performed, little is found except signs of acute nephrosis, indicating absorption of toxin. McClelland has observed similar types of patients in the mines of northern Ontario. Transfusion has been used as treatment, but it has not benefited them. The different types of intravenous therapy which are being used now for shock have been of no avail, but some of the patients have been given sodium bicarbonate intravenously in fairly large quantities which seems to help.

O'Crowley⁴⁶ states, in discussing Hamer and Mertz's article on anuria, that within the past year he had under his care in the hospital 2 men in their thirties who had been subjected to the fumes of carbon tetrachloride from cleaning preparations. They had anuria when they were brought into the hospital. After they had been watched a little while they showed the picture typical of anuria due to poisoning with chemicals. One allowed a double decapsulation, and the other refused. The one with the decapsulation died in three days, the other died in three weeks. But he established an adequate output of urine with an absolute to zero specific gravity during that time. O'Crowley thought the problem was settled at that time. One patient could get along without decapsulation, and the other had to have it, but they both died.

Shupe,⁴⁷ in discussing Hamer and Mertz's article on anuria, reports a case in which the treatment may give some clue to the handling of cases of acute nephritis from toxic material, from whatever cause, either mercury bichloride or toxic material from contusion. This was the case of a man suffering from poisoning with mercury bichloride. Just how much mercury bichloride the patient had absorbed was not known, but the concentrations of urea, nitrogen and creatinine in his blood were high. He was treated by multiple transfusions two a day with bleeding each time. That is, about 200 cc of blood was removed and about 400 cc put in. He was given sodium bicarbonate intravenously. One kidney was decapsulated, the other kidney was left alone. The patient recovered. Postoperative retrograde pyelograms were made and showed the kidney that was decapsulated in much better functioning condition as to the appearance of the pyelogram and the output of indigo carmine than the kidney that had not been decapsulated.

Jeck⁴⁸ states, in discussing Hamer and Mertz's article on anuria, that Dr. John Rogers, in his experimental work on dogs, noticed that thyroid residue, one of

45 McClelland, J. C., in discussion on papers of Hoch, Rathbun,⁹ Smith and Strasberg³⁰ Hamer and Mertz⁴⁴ and Ormond, Wadsworth and Morley, *Tr. Am. A. Genito-Urin. Surgeons* **35** 185-186, 1942.

46 O'Crowley, C. R., in discussion on papers of Hoch, Rathbun,⁹ Smith and Strasberg³⁰ Hamer and Mertz⁴⁴ and Ormond, Wadsworth and Morley, *Tr. Am. A. Genito-Urin. Surgeons* **35** 188-189, 1942.

47 Shupe, T. P., in discussion on papers of Hoch, Rathbun,⁹ Smith and Strasberg,³⁰ Hamer and Mertz⁴⁴ and Ormond, Wadsworth and Morley, *Tr. Am. A. Genito-Urin. Surgeons* **35** 189, 1942.

48 Jeck, H., in discussion on papers of Hoch, Rathbun,⁹ Smith and Strasberg³⁰ Hamer and Mertz⁴⁴ and Ormond, Wadsworth and Morley, *Tr. Am. A. Genito-Urin. Surgeons* **35** 189-190, 1942.

the substances he was using, was a great stimulator of the kidney. Rogers advised the use of thyroid residue in cases of anuria, presumably of the excretory type. Shortly after this, a patient who had a single kidney was admitted to the urologic service at Bellevue Hospital. He had had anuria for about five days when he came in. Some of the thyroid residue was procured and given to him according to Dr. Rogers' instructions, and within twelve hours he was excreting large quantities of urine.

ORTHOSTATIC ALBUMINURIA

Young, Haines and Prince⁴⁹ discuss orthostatic albuminuria and the importance of its recognition by medical examining boards. They report in detail the case histories of 4 patients who had been rejected by the medical examining boards of either the Army or the Navy because of the presence of albumin in the urine. In each of these cases it was established by careful clinical and laboratory tests that the albuminuria was orthostatic and that no renal lesion was present. As a result of their reports, the examining boards which previously had rejected these men accepted them. In the presentation of these 4 cases the clinical and laboratory tests which have been found valuable are discussed, the diagnostic value of placing the patient in an exaggerated lordotic position being emphasized.

Sixty-seven cases in which the condition was diagnosed as orthostatic albuminuria were also studied from the records of the Johns Hopkins Hospital. Three of these were shown to be cases of definite nephritis and have been excluded from the analysis. In the remaining 64 cases no evidence of nephritis has developed with the passage of time, and repeated examinations of some of the patients have shown their urine to be free from albumin at various periods after their admission to the Johns Hopkins Hospital. These studies show definitely that orthostatic albuminuria is a harmless condition which eventually disappears, generally early in adult life.

Before a diagnosis of orthostatic albuminuria is made, the following criteria should be met: (1) no past history of renal disease, (2) normal chemical composition of the blood (nonprotein nitrogen, blood urea, total protein and albumin-globulin ratio), (3) normal renal function (phthalein, urea clearance, and dilution and concentration tests), (4) no leukocytes, erythrocytes or casts in the urine except intermittently and in small numbers, (5) no elevation of the blood pressure, (6) negative plain roentgenograms and intravenous urograms, (7) absence of albumin in the urine secreted and voided when the patient is in the recumbent position.

There are a considerable number of cases of orthostatic albuminuria, and many persons have been rejected by medical examining boards because of the presence of albumin in the urine. With the more comprehensive tests which have been outlined, many of these men probably could have been shown to be fit for service. It would seem desirable for draft boards to reopen the records of these men and subject patients who have been rejected because of albuminuria to additional tests.

Young, Haines and Prince avoid any discussion of the subject of so-called benign albuminuria, not orthostatic, of which many cases are reported, and concerning the significance of which there is considerable difference of opinion.

⁴⁹ Young, H. H., Haines, J. S., and Prince, C. L. Orthostatic Albuminuria. The Importance of Its Recognition by Medical Examining Boards. *Mil. Surgeon* 92:353-365 (April) 1943.

TESTICLE

Cryptorchidism—Young⁵⁰ presents an intra-abdominal operation for cryptorchidism and reports a case

The patient was 34 years of age. Through a median abdominal incision the pelvis was thoroughly explored. There were no tubes or uterus present. On each side a vas deferens was plainly visible beneath the peritoneum as it coursed upward from the posterolateral wall of the bladder on each side over the pelvic brim across the vessels, above which it joined an elongated spreadout epididymis which ended in a small testicle that projected into the abdominal cavity. The testicle was covered by peritoneum. The situation was identical on the two sides. The testicle lay about 5 cm from the middle line and was held in this position by a fatty cord about 8 mm in diameter which ran upward toward the kidney.

The vas deferens was exposed extraperitoneally by simply separating the peritoneum from the abdominal wall and following this into the pelvis by the side of the bladder, then upward along the lateral wall of the pelvis, following the vas deferens. The testicle was drawn down to the region of the internal inguinal ring. The gubernaculum was divided, completely liberating the cord and the vessels. The finger of the right hand was then inserted above the iliac vessels through a depression which was recognized as the internal ring. Through this the finger was easily pushed until it was visible beneath the skin covering the groin. An oblique incision was made over the finger, which was then brought out through the incision. A clamp was then inserted through the inguinal incision and internal ring and grasped the fatty cord below the testicle. Traction was made, and the testicle, epididymis, vas and veins were drawn out through the inguinal incision. The cords were found to be sufficiently long to allow transplantation to the bottom of the scrotum. Another finger then was inserted into the inguinal canal and turned downward so as to pass out through the external inguinal ring, which was thus greatly dilated, and on down into the scrotum until the lowest part of this had been reached.

This having been accomplished, an incision was made over the finger tip within the scrotum through its lateral wall. The thigh was pushed up by an orderly to a flexure of about 45 degrees, and an incision was made on its inner side opposite the scrotal incision. The fascia lata was exposed. The fatty cord, which was still attached to the testicle, was then caught and drawn down through the external ring into the depth of the scrotum and out through the scrotal incision. No difficulty was experienced in approximating the fatty cord to the fascia lata with sutures of chronic catgut. This held the testicle in the lowest portion of the scrotum, which was then sutured to the edges of the incision in the thigh with catgut. On the left side the technic was similar to that already described.

Three weeks later a second operation was done. The scrotum was liberated from the thigh on each side by dividing the anastomosed skin and the fatty cord which ran from the testicle to the fascia lata. The scrotal incision was closed on each side with interrupted sutures of fine silver wire. The incisions in the thigh were similarly approximated.

Young stresses the value of the intra-abdominal operation in facilitating the freeing of the testicle and its cords and the satisfactory performance of orchidopexy. He believes that when cryptorchidism is intraperitoneal on both sides the operation carried out through a midline abdominal incision with extraperitoneal exposure and freeing of the testicle offers manifold advantages. He believes that the same

⁵⁰ Young, H. H. An Intra-Abdominal Operation for Cryptorchidism. *Trans Am Urol Surg Soc* 35:115-119, 1942.

technic would also be satisfactory even for cryptorchid testes much lower within the abdomen, as the intra-abdominal extraperitoneal exposure of the gonad and cords gives a far better chance to free the restricting bands without injuring the vascular supply. In a good many cases Young has employed flexion of the thigh to avoid too great tension on the cord after the modified Torek operation. After two weeks the pillows are removed from beneath the knees and the thighs straightened out. The patient is out of bed at the end of the third week. Extension and flexion of the thighs are usually carried out to increase the low position of the transplanted testicle. This swinging motion of the lower extremity, with the patient in the standing position, is carried out several times daily until the time when the scrotum is detached from the thigh.

Lapin, Klein and Goldman⁵¹ report on 200 boys treated in their endocrine clinic for cryptorchidism in the last nine years. Thirty-nine were given endocrine treatment and followed from two to nine years. Apparent success in 14 cases (35.9 per cent) is reduced to success in only 6 cases (15.3 per cent) by the omission of cases in which treatment was not given, cases in which descent of the testis was only partial and cases in which hypogonadism ensued, in 1 of which there is complete azoospermia. In 11 cases in which endocrine treatment failed powdered sterile chorionic gonadotropin was implanted or operation was performed, or both.

Conclusions reached from these cases and a study of the literature are as follows. Treatment of cryptorchid testes is advisable to relieve the deficiency of formation of androgenic hormone and of spermatogenic activity and the psychologic handicap, provided a procedure is adopted to minimize the dangers of pubertas precox, of osseous retardation and of testicular atrophy. The optimal age for treatment is 14 years. A preliminary test of endocrine therapy is fully justified in any case of cryptorchid testes not clearly ectopic. Chorionic gonadotropin is the only substance free of theoretic objections. The maximal amount of chorionic gonadotropin given should not greatly exceed 6,000 international units. This amount should be given in small, frequent doses over a six week period without any rest interval.

If cryptorchid testes do not descend after the administration of 6,000 international units of chorionic gonadotropin in a six week trial period, operation should be immediate, and further gonadotropin can be given after the testis is embedded in the scrotum.

Ectopic testes should benefit from a similar preoperative and postoperative administration of chorionic gonadotropin, except when complicated by a substantial inguinal hernia.

TUMOR OF THE EPIDIDYMIS AND TUNICA VAGINALIS

Mackay⁵² presents 2 cases of tumors involving the tunica vaginalis and epididymis. In reviewing the literature, similar cases were found to have been reported and classified as instances of cavernous lymphangioma, adenoma and carcinoma. In 1 of MacKay's cases the tumor had been present for twenty-two years, and in the other, for three years. It is his conviction that these tumors are mesotheliomas of the tunica vaginalis derived from the cells lining the serous cavity and are probably benign.

51 Lapin, J. H., Klein, W., and Goldman, A. Cryptorchidism, *J. Pediat.* 22:175-188 (Feb.) 1943.

52 Mackay, C. H. Tumors of the Epididymis and Tunica Vaginalis. Report of Two Cases. *J. Urol.* 49:440-443 (March) 1943.

VASITIS NODOSA

Benjamin, Robertson and Cheetham⁵³ state that in most instances beading of the vas deferens has been associated with tuberculosis of the genital tract. They have studied a case of nontuberculous beading of the vas unlike any observed in a search of the literature and in a study of stained sections of many normal and pathologic vasa.

The patient had felt "lumpy" areas in the cord, and he also noticed that these nodular areas were tender and enlarged after intercourse. The vasa, on examination, were interesting in that the beading or nodularity was not dissimilar to that found in tuberculosis. The nodules were small, round, firm and adherent to the vasal wall. They were approximately half the diameter of a lead pencil. As one gently passed one's finger over them, one gained the impression that one could be feeling hemispheres of tiny glass beads. The nodules were larger and more numerous as one approached the epididymis. The epididymides and testes were normal. Cystoscopy revealed that the bladder, ureteral orifices and prostatic urethra were normal.

With the patient under pentothal sodium anesthesia an incision was made over the left spermatic cord. The tissues about the vas deferens were firmly adherent to it, indicating perivasitis. The vas was then freed from the epididymis to the external inguinal ring. The surface of the vas showed many small, grayish white, firmly fixed nodules, which varied in size. The epididymis and testis were normal. A small piece of the vas deferens near the epididymis containing several palpable nodules was removed for study. A frozen section did not show any evidence of a tuberculous lesion. An end to end anastomosis of the vas was carried out with chromic catgut 000 being used in an atraumatic needle. The pathologic report on the gross specimen stated that the left vasal wall was thickened and that the tissues about it were firmly adherent. The frozen section showed what appeared to be epithelial lined spaces, some containing spermatozoa and others none.

Benjamin, Robertson and Cheetham⁵³ discuss four possible etiologic factors—faulty development, infection, diverticula and cyst formation. Since the nodularity was associated with a definite inflammatory reaction, they suggest the term "vasitis nodosa."

PEYRONIE'S DISEASE

Wesson⁵⁴ states that the nonvenereal prostatitis of youth and the plastic induration of later life are both due to the same violation of nature's sex laws.

A prolonged virulent inflammation of the urethra may result in Peyronie's disease. It may be fundamentally due to (1) heredity, (2) degenerative disease of middle or late life, (3) fibroplastic diathesis or (4) trauma. "Internal trauma" from prolonged ungratified sexual desires or external trauma from lack of proper sexual cooperation is the direct cause. The approaching menopause with the concomitant frigidity of the consort is probably indirectly the principal cause of plastic induration.

In the early stages of the disease, before the deposit of lime salts, diathermy, fortified by disodium phosphate by mouth, may not be a specific, but it is inexpensive and harmless and keeps up the patient's morale. Without treatment the lesion may regress, but it usually advances and ultimately invades the corpora cavernosa.

⁵³ Benjamin J. A., Robertson T. D. and Cheetham, I. G. Vasitis Nodosa. A New Clinical Entity Simulating Tuberculosis of the Vas Deferens, *J. Urol.* 49: 575-582 (April) 1943.

⁵⁴ Wesson, M. B. Peyronie's Disease (Plastic Induration). Cause and Treatment. *J. Urol.* 49: 350-356 (March) 1943.

Volavsec⁵⁵ reports 198 cases of plastic induration of the penis. As a result of observation of many cases, Volavsec believes this condition is due to a reaction of the connective tissue system to local hypertrophic and shrinking processes. In addition to this, there are various irritative factors, such as mechanical trauma, atrophy and fibrosis of the lining membranes. There is quite possibly a hereditary influence also in this condition, as in 4.6 per cent of all cases the induration associated with the digital deformity known as Dupuytren's contracture, which unquestionably is a hereditary or familial disease. In 34 per cent of the cases in which there was Dupuytren's contracture there was also plastic induration of the penis. In a series of cases in which radium was used, there was complete cure in 32.8 per cent and partial reduction of symptoms in 47 per cent, while in 20 per cent the condition was not influenced at all. In those cases in which calcification and ossification occur, Volavsec suggests surgical removal of the occlusions, although he admits that radium gives the most satisfactory results.

UROGRAPHY

Pendergrass and his associates⁵⁶ record 26 deaths following the administration of contrast mediums in 661,800 instances (0.0039 per cent). Ten of these deaths were classified as immediate and 16 as delayed. Eleven fatalities have previously been reported. Seven of these were immediate and 4 delayed.

The immediate deaths followed the intravenous injection of diodrast, and the majority were preceded by symptoms simulating those of anaphylactic shock, although the deaths may not have been due to an "anaphylactoid reaction." Overdosage may have been the cause of other deaths. In the cases of delayed death the contrast medium had not been proved to be an etiologic factor. Toxic reactions may occur, especially among patients who have had previous renal damage and reduction of excretion of urea.

No immediate deaths have been reported following retrograde pyelography with any of the contrast mediums.

Hypersensitivity simulating anaphylactic shock was reported 77 times by radiologists and 55 times by urologists. These figures probably represent an exaggerated incidence, as Pendergrass and his associates believe that in several instances true shock had not occurred. This type of reaction was reported from the drugs diodrast, diodrast compound, iopax, neoiopax and skiodan. In many instances of true shock the physicians expressed the opinion that only the prompt administration of epinephrine saved the patient's life.

Many patients also showed nonfatal reactions, either local or general such as flushing, nausea, vomiting, urticaria (local or generalized), itching, venospasm, pain in the shoulder, sense of constriction in the larynx, phlebitis, unconsciousness (occasional), tetany or cerebral irritations.

It is advised that contrast mediums are contraindicated for patients suffering from severe hepatic disorders, nephritis, exudative diathesis (in children) and severe uremia. They should be used with caution in cases of pulmonary tuberculosis or of hyperthyroidism and in cases in which a reduction of blood pressure would be dangerous.

55 Volavsec W. Zur Kenntnis der Induratio penis plastica. *Ztschr f Urol* 35 173-178 1941

56 Pendergrass, E. P., Chamberlin, G. W., Godfrey, E. W., and Burdick, E. D. A Survey of Deaths and Unfavorable Sequelae Following the Administration of Contrast Media. *Am J Roentgenol* 48 741-762 (Dec) 1942

Deaths have followed the use of intravenous contrast mediums for patients who had only one kidney. On the other hand, some observers with large experience state that they have never encountered any reactions among such patients. Pendergrass and his associates advise studying the chemical composition of the blood before subjecting these patients to intravenous injections of contrast mediums.

Caution should be observed in dealing with patients who have had repeated injections of contrast mediums. Many injections have been done without mishap, but some have resulted in severe reactions at later injections.

Pendergrass and his associates believe that contrast mediums should not be withheld in cases of hypertension unless there is evidence of severe renal damage.

No patients who have significantly impaired renal function should be accepted for intravenous pyelograms, and no more than a single injection of 50 cc of 70 per cent solution of diodast should be given to a patient on any day.

Administration of solution of epinephrine hydrochloride (1:1,000) in a dose of from 0.3 to 0.5 cc is offered as a prophylactic measure immediately before injection of the contrast medium is begun for patients giving a history of allergy. It is advised that when taking a history of allergy one should ask specifically about asthma, hay fever, rose cold, sensitivity to drugs and eczema in childhood. The history should include not only that of the patient but that of his family. Pendergrass and his associates state that Kern believes that the patch test may be the most reliable of the various methods but the mouth test may also warn of sensitivity. Since some of the reactions occur eighteen hours after the test and since it is more convenient, it is advisable to make the test the day before urographic study. The intradermal test has been used extensively, but the conjunctival test has been preferred by some. According to the literature, some think the intradermal test of value but others believe it is of no help. Apparently the conjunctival test is harmless, and it may reveal extreme sensitivity.

Tzschirntsch⁵⁷ discusses injuries following retrograde pyelography, with particular attention to the damage of the renal parenchyma caused by exerting high pressure on the renal pelvis and the injury to the renal mucosa produced by either corrosion of the surface layer or absorption of the medium itself. The most common and the most provable roentgenologically is the definite damage of the renal pelvis and calices by trauma from the ureteral catheter.

Tzschirntsch describes 2 cases in which damage to the kidney occurred after the introduction of the catheter, proved in both instances by roentgenologic examination and surgical exploration. In both cases there was a perforation of the mucosa of the calices with deposition of contrast medium in the renal parenchyma. In 1 case there was great destruction of tissue with later sclerosis of the involved region. In the other complete resorption of the material occurred but renal stones developed several years later. In each case there were the same symptoms—sharp pain at the time of injection of a small amount of medium and serious renal symptoms for several days afterward.

Tzschirntsch states that perforation of this kind can be avoided by using the catheter without a stylet. The ureteral catheter should be inserted only into the lowest part of the pelvis. The length of the catheter inserted should be controlled by watching the scale of markings on the catheter and the rate of dripping of urine from the ureteral catheter.

⁵⁷ Tzschirntsch, K. Die instrumentelle Schädigung der Nieren durch die retrograde Pyelographie, *Ztschr f Urol* 35:69-77, 1941.

SULFONAMIDE AND PENICILLIN THERAPY

Strauss and Grunstein⁵⁸ report a study of 615 hospitalized gonorrheal patients which shows that 60 grains (4 Gm) of sulfathiazole daily for one week gave an apparent cure rate of 95 per cent. The administration of sulfathiazole or sulfapyridine to the patients not cured by the first course of treatment increased this rate to 98.9 per cent.

It must be determined whether the criteria of cure employed are sufficient to insure protection of the public against further infection. The difficulty of detecting the asymptomatic carrier cannot be emphasized too strongly. A prostitute, although treated, remains potentially infectious for approximately three months, during which time, if at large, she is a source of infection and as such forfeits her right to the benefit of doubt. The cure of an infected prostitute requires adequate compulsory hospitalization. Repeated offenders should be interned for the duration and compelled to aid in the war effort. If the law now does not adequately remove this public health hazard, as it does with most contagion, remedial statutes should be enacted at once toward that end. If the state can call on a man for his life in this grave emergency, surely the common welfare demands that the "right" of an infected prostitute to be at liberty while still infectious be disallowed, at least for the duration of the war.

Herrell, Cook and Thompson⁵⁹ have studied experimentally the antibacterial activity of penicillin against several strains of *Neisseria gonorrhoeae* isolated from patients in whom the infection was completely resistant to adequate treatment with sulfonamide preparations. These strains of organisms are inhibited completely in fairly high dilutions of an active form of penicillin. Bacterial cultures reveal that the number of organisms is decreased greatly at the end of one or two hours' contact with penicillin. Between the second and third or the third and fourth hours of contact with penicillin no viable organisms were found. This experimental evidence immediately suggests that penicillin should prove effective in the treatment of clinical infections due to these bacteria that are resistant to sulfonamide compounds.

The complete absence of toxicity following the intravenous administration of pyrogen-free penicillin, the lack of any discomfort to the patient and the rather rapid disappearance of clinical symptoms have been observed in 3 cases of sulfonamide-resistant gonorrheal infections. Because of the limited amounts of penicillin available, penicillin therapy should be reserved and studied further in those cases in which the infection is resistant to the accepted forms of treatment now being used. In all the cases reported, in addition to the clinical response noted, negative bacterial cultures were obtained some time between seventeen and forty-eight hours after the institution of penicillin therapy.

Barnes and Kawauchi⁶⁰ state that the most important factors influencing the formation of urinary concretions of sulfonamide compounds are (1) concentration of the drug in the urine, which may be reduced by decreasing the dose and increasing the fluid intake, (2) degree of acetylation of the sulfonamide compound, which cannot be influenced by extrinsic means, (3) urinary stasis, which is over-

58 Strauss H, and Grunstein, I. Sulfathiazole Therapy of Five Hundred Prostitutes with Chronic Gonorrhea. The Control of Venereal Disease in Wartime, *J A M A* **121** 1187-1190 (April 10) 1943.

59 Herrell W E, Cook, E N, and Thompson, L. Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections. *J A M A* **122** 289-292 (May 29) 1943.

60 Barnes R W, and Kawauchi G K. Factors Influencing the Formation of Sulfonamide Urinary Concretions. *J Urol* **49** 324-330 (Feb) 1943.

come by establishing and maintaining free drainage, (4) p_H of the urine, which may be adjusted, (5) temperature, which may be elevated

Barnes and Kawaichi's experimental work shows that as the p_H of the urine is increased and the temperature of the urine elevated, the solubility of sulfathiazole and sulfadiazine is heightened. This range is from a concentration of sulfathiazole of 78.1 mg per hundred cubic centimeters at a p_H of 5.0 and temperature of 78.8 F to a concentration of 250.0 mg per hundred cubic centimeters at a p_H of 8.0 and temperature of 105.0 F. The range for sulfadiazine is from 69.6 to 170.4 mg per hundred cubic centimeters. The danger from concretions of sulfonamide compounds can be reduced by rendering the urine more alkaline and by elevating the temperature. Anuria from sulfonamide concretions occurs much more frequently in the Oriental than in the white race, the reason for this is not known.

Jeck and Orkin⁶¹ state that therapeutic enthusiasm for the use of sulfonamide preparations has often been tempered by the accompaniment of a disturbingly high incidence of toxic reactions and formation of calculi in the urinary tract, with or without anuria. Pharmacologic investigation has shown the readiness with which the free form of sulfadiazine is concentrated in the blood, its comparatively slow excretion and its greater solubility in the urine. Sulfadiazine is regarded by many physicians as innocuous, and chiefly for that reason it is considered the ideal drug of the sulfonamide group. On the other hand, sulfadiazine, like its relatives having the radical of the parent compound, may under certain circumstances cause toxic reactions, and such reactions occasionally are severe.

In experiments on the albino rat, the toxicity of sulfadiazine was investigated with especial reference to renal lesions. A strikingly high incidence of renal damage was found after the injection of fatal doses of sodium sulfadiazine, which was explained as due to the poor solubility of the free drug, which may be precipitated in the convoluted renal tubules. Because of the poor solubility of sulfadiazine, obstruction of the kidney by the precipitation of this compound may be of long duration and may lead to a severe calcifying nephrosis. These findings indicate that the tendency for the retention of the free sulfadiazine in the circulation increases with impairment of renal function and do not suggest that renal damage will be less likely to occur from the use of sulfadiazine than from the other sulfonamide compounds, as has been hitherto reported.

The more recent clinical reviews of sulfadiazine in treatment of pneumonia have shown a greater frequency of the toxic renal effects than was at first reported.

During the past six months at Bellevue Hospital, sulfadiazine has been used extensively, supplanting sulfathiazole in the treatment of pneumonia. The clinical results have been in large measure excellent, but the urologic service has been called into frequent consultation because of the complications which have followed its administration. Jeck and Orkin have observed more than 35 cases in which crystals of acetylsulfadiazine were found in the urine, but apart from an occasional mild colic and microscopic hematuria the patients soon recovered completely. It should be remembered, however, that crystals are of no particular significance except in freshly voided warm urine. Jeck and Orkin have been more concerned over 10 patients (seen in consultation by the urologic service), all of whom had severe toxic reactions following the use of the drug. Seven of these patients recovered, 3 died.

61 Jeck, H. S., and Orkin, L. A. Toxic Renal Reactions Following the Use of Sulfadiazine, *Tr Am A Genito-Urin Surgeons* 35:1-14, 1942.

In the analysis of these 10 cases, which are reported in detail, Jeck and Orkin's chief objective has been not to determine the relative frequency of severe toxic reactions following the use of sulfadiazine but merely to report that they do occur. In this series the drug was used in the treatment of 5 men and 5 women, the ages varied between 52 and 93 years, the clinical diagnosis in 9 cases was bronchopneumonia or lobar pneumonia and in 1 case fracture of the femur. In all cases there was associated arteriosclerotic heart disease, with varying degrees of congestive failure.

The route of administration of the drug in all cases was oral, although in 2 cases intravenous administration was also employed. One patient received 32 Gm of sulfathiazole before sulfadiazine was given. The initial dose, as a rule, was 2 Gm followed by 1 Gm every four hours. The time of onset of the major toxic symptoms varied from three to twenty-one days, and in 2 instances they appeared three and five days after the discontinuance of administration of the drug because of minor toxic symptoms. The total amount of drug administered up to the time of appearance of the symptoms varied from 12 to 128 Gm. This would seem to indicate that severe, and even fatal, reactions might occur with as little as 12 Gm in as short a time as three days. A study of the intake of fluid and urinary output in this series would perhaps indicate that in most cases sufficient attention was not given to these features. It is of vital importance to force fluids to 2,000 cc throughout the administration of the drug, and to note carefully the urinary output, so that it will not be allowed to fall appreciably. Two of the patients showed an elevated nonprotein nitrogen content on admission, and in all cases there was definite elevation of the nonprotein nitrogen at the toxic point, the values varying from 40 to 180 mg per hundred cubic centimeters. The recorded concentrations of sulfadiazine in the blood varied from 12.2 to 32.2 mg.

It is interesting to note that the patient having a blood sulfadiazine level of 12.2 mg per hundred cubic centimeters and a nonprotein nitrogen content of 64 mg died in anuria, while the patient with a sulfadiazine level of 23.2 mg and a nonprotein nitrogen content of 180 mg (the highest in the series) recovered.

The treatment employed in those cases in which there was anuria or suppression, gross hematuria or increasing uremia was to stop administration of the drug at once. That concretions may exist without blocking the ureters has been demonstrated by many investigators. Under these circumstances the treatment of hematuria due to sulfadiazine by means of forcing fluids alone seemed adequate since there is evidence that the concretions may be dissolved or washed out. If, however, complete anuria or suppression occurred or if the possibility of a unilateral obstruction seemed evident, cystoscopic examination was done at once. Both ureters were catheterized, and the catheters were left in place and irrigated every hour or two for at least two to three days. In most cases in which the obstruction had been overcome, adequate drainage established and fluids forced, the blood level and nonprotein nitrogen content fell and the patient recovered.

In those cases in which there is even the slightest question of obstruction due to calculi or crystals in the urinary tract (especially in the ureters), cystoscopy and probably ureteral catheterization should be performed without any hesitation.

Satterthwaite⁶² states that sulfadiazine has a lower toxicity than other sulfonamide compounds in common use, but it also exhibits a characteristic pattern of toxic reactions. He presents an analysis of 58 toxic reactions occurring in a series

62 Satterthwaite, R. W. Sulfadiazine Reactions. Their Frequency and Treatment in Urological Cases, *J. Urol.* 49: 302-315 (Feb.) 1943.

of 500 cases (11.6 per cent). All of these toxic reactions yielded promptly to treatment, which usually consisted of stopping use of the drug and forcing fluids. The toxic reactions were usually multiple and were as follows: temperature reactions, 12 cases; conjunctivitis, 3; arthritic pain, 3; severe anorexia, 2; itching, 2; dizziness, 4; severe disorientation, 6; severe nausea, 16; severe nausea and vomiting, 5; headache, 11; dermatitis, 4; hematuria, with or without urinary concretions and renal colic, 6; leukopenia, 19; and partial suppression of the urinary output, 2.

Toxic reactions are prevented by moderate dosage, limiting the duration of therapy, close observation of the blood level of sulfadiazine, especially when the renal function is impaired, and a careful check of the leukocyte count at least every third day throughout the duration of treatment. Leukopenia, the most severe reaction observed with sulfadiazine therapy, develops not earlier than the third day and usually in the second week of treatment. Giving the patients a printed set of precautions to observe has reduced the incidence of toxic reactions.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1942

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN
ACADEMY OF ORTHOPAEDIC SURGEONS

XVI CONDITIONS INVOLVING THE HIP JOINT

Marshall⁴³³ presents a nonoperative therapy for tuberculous and other low grade inflammatory diseases of the hip joint. He believes that when there is roentgenologic evidence of disease either in the acetabulum or in the head of the femur the tendency to aim at ankylosis is wrong. During a ten year period he treated this type of infection of the hip in accordance with Rollier's method. The general principle of the treatment is rest and immobilization during the acute stage of the disease, followed by gradual resumption of movements with support. In cases in which erosion of the acetabulum or the femoral head develops, traction is continued for eighteen months to two years, with roentgen examinations at six month intervals. Weight bearing is then permitted, an appliance being used which is a Thomas type of walking caliper fitted to a pelvic belt of celluloid to which is fastened a metal plate with an attached spring which exerts an abducting force and controls rotation. A corrective diet high in vitamin and calories is maintained plus solar ray irradiation. Fourteen cases are presented in detail, all of low grade tuberculous or nonpyogenic processes. Good functional results are reported.

Milch⁴³⁴ describes an apparatus for measurement of the degree of contracture of the hip. The author criticizes the present practice of placing the patient in a supine position and flexing the unaffected leg until, in the opinion of the examiner the lumbar curve is obliterated. He shows that the amount of extension of the hip depends on the forward tilt of the pelvis, which, in turn, depends on the relative length of the pelvifemoral ligaments and on the lordosis of the lumbar portion of the spine. The author has devised a flexible metal device to fit along the upper edge of the Nelaton area, with a bar to run vertically down the thigh. The patient is measured in the upright position.

In a preliminary report Baker and Waters⁴³⁵ present their experiences with vitallium cup arthroplasty of the hip for ankylosis, based on a study of end results in 15 patients, 3 of whom had bilateral operations. Five of the patients were women, and 10, men. Most of the patients were in their third or fourth decade. The follow-up period ranged from eight to fourteen months. Grading of end results was determined by the extent of functional recovery and, in particular, by evaluation of the patient's subjective reaction to his result. Little if any correlation was found between the cause of the ankylosis and the type of end result. There was noticed in many of the hips a tendency to resume the typical abduction-flexion deformity, with progressive reduction in the immediate postoperative mobility. Stressed are the needs for an adequate period of hospitalization and for intelligent cooperation in after-treatment. The operation is thought particularly profitable to bedridden and badly crippled persons. Because of the relatively small number of cases the authors do not feel justified in drawing definite conclusions.

433 Marshall D. V. Treatment of Coxitis. *J. Bone & Joint Surg.* **24** 169-184 (Jan.) 1942

434 Milch H. Pelvifemoral Angle. Determination of Hip-Flexion Deformity, *J. Bone & Joint Surg.* **24** 148-153 (Jan.) 1942

435 Baker L. D. and Waters C. H. Jr. Vitallium Cup Arthroplasty of Hip. *Arch. Surg.* **44** 531-542 (March) 1942

A new operation, femoroischial transplantation, is presented by Bosworth⁴³⁶. It is designed to secure stability of the hip and arrest of disease through bony fusion in conditions in which the head and the neck of the femur have been extensively destroyed, and as a result the use of standard methods for obtaining fusion is precluded. Statistical data of 9 tuberculous patients on whom the operation was performed are given in detail. The operation consists of an oblique osteotomy of the femoral shaft in the subtrochanteric region and placing of the proximal end of the distal portion into a denuded bed in the lateral aspect of the ischium. In the presence of sinuses, a preliminary operation eradicating the diseased portion of the hip is often indicated. The functional, cosmetic and weight-bearing results do not differ materially from the result of fusion of the hip joint proper.

A series of 71 surgically treated adult patients with painful hips caused by hypertrophic changes were reviewed by Ghormley and Coventry⁴³⁷. Comparison was made between this series of patients treated from 1938 to 1940, inclusive, and an earlier similar series of 77 patients treated surgically, reported by Henderson and Pollock of the same clinic during a previous ten year period. Notable in the comparison have been the following trends: (1) to abandon manipulation, (2) to decrease the number of drilling operations, (3) practically to abandon cheilotomy, (4) to decrease the number of reconstruction operations, (5) to increase the use of acetabuloplasty, (6) to increase the number of arthrodeses, and (7) to increase the use of arthroplasty.

The authors carefully stated that they do not mean to convey the idea that treatment in all such cases of painful hips should be surgical. It is their opinion that surgical treatment holds more promise of improvement or relief in properly selected cases than does conservative treatment. They support their contention by comparing surgical results with results in a fairly comparable parallel series of 116 cases they observed from 1938 to 1940, inclusive, in which the usual conservative measures were used. Their experience indicates that relief of pain is most certain to be obtained by arthrodesis, though they pointed out its contraindications in bilateral involvement and in arthritis of the lumbar portion of the spine.

Hark⁴³⁸ presents a resume of the modern methods of treating separation of the upper femoral epiphysis. He divides treatment into two classes, closed manipulation and surgical reduction. He notes that the roentgen examination may deceive the physician if internal rotation is carried too far. With minimal displacement, he prefers to drill or to wire the epiphysal line and allows five months for complete fusion. With moderate displacement of the head, he advises subtrochanteric osteotomy through an anterior or a lateral incision, followed by immobilization, with the leg in abduction and internal rotation. For severe displacements, the author recommends that an open operation be done, with repositioning of the femoral head, held in place by some metal fixation, such as a wire, a Smith-Petersen nail or a bone graft. A fixed traction cast is then applied until the healing is complete.

In convalescence, if roentgenologic evidence shows that healing has taken place and that no necrosis of the head has occurred, active exercise is allowed and the heel of the well leg is elevated. Weight bearing is not allowed for a year and the well hip is always carefully observed to discover whether a similar process is beginning there.

⁴³⁶ Bosworth, D. M. Femoro-Ischial Transplantation. *J. Bone & Joint Surg.* **24**: 38-46 (Jan.) 1942.

⁴³⁷ Ghormley, R. K. and Coventry, M. B. Surgical Treatment of Painful Hips of Adults. *J. Bone & Joint Surg.* **24**: 424-428 (April) 1942.

⁴³⁸ Hark, F. W. Treatment of Separation of Upper Femoral Epiphysis. *S. Clin. North America* **22**: 119-134 (Feb.) 1942.

Lipscomb and Chatterton⁴³⁹ present reports of 5 cases of involvement of the acetabular centers of ossification in young patients. In 3 of these cases there were acetabular changes without involvement of the femoral head and in 2 acetabular changes with involvement of the adjacent head of the femur.

These authors review the anatomic features of the hip area as well as the structure, embryologic aspects and development of the centers of ossification. They believe that the disturbance seemed to have been in the primary centers and that, since the superior or weight-bearing surface of the acetabulum was chiefly involved, the iliac center appeared most likely to be affected.

Milch⁴⁴⁰ discusses in detail the various mechanical factors involved in performing an osteotomy of the upper part of the femur. He describes an "abduction osteotometer," with which the pelvis, hip joints and femurs may be simulated, with any degree of deformity, through the use of which the osteotomy may be accurately planned, and the most desirable level and angle determined for restoration of the mechanical axis of the femur.

Reed and Sosman⁴⁴¹ briefly review the usual data in Gaucher's disease and report in detail an atypical case of this unusual condition. Their patient had been subjected to two operations after a diagnosis of osteomyelitis, which must always be differentiated, but was unlike the usual picture in that the spleen could not be palpated, although roentgen examination revealed it to be enlarged. Roentgen examinations were suggestive but not typical of this disease, and biopsy of a specimen of bone was necessary to prove the presence of Gaucher cells, no evidence could be found of the presence of the disease by careful roentgen examinations of 7 other members of the patient's immediate family.

Schein and Arkin⁴⁴² stress the importance of early recognition of involvement of the hip joint during childhood in patients with Gaucher's disease. The authors report 8 cases in which the pathologic processes were noted out of 19 verified cases of Gaucher's disease. The skeletal changes are attributed to the infiltration and the replacement of trabeculae of the bone by kerosin-bearing reticulum cells. These lesions appear on roentgenograms as translucent or more radiotransparent areas and account for the characteristic mottling. In children the lesion apparently resembles chronic osteomyelitis, tuberculous coxitis and Legg-Perthes disease. In the adult the involvement takes the form of considerable coxa vara deformity with variable degrees of osteoarthritis.

The authors believe that when the involvement of the hip is noted during childhood conservative therapy in the form of rest and immobilization of the affected leg is in order, since a condition rather similar to Legg's disease exists. In 2 cases favorable results are reported to have followed conservative therapy.

Zimmerman,⁴⁴³ serving as a medical examiner in the Medical Corps of the United States Army, has found that 3 of 5 men examined have a tilt of the pelvis, with or without scoliosis. About a fourth of this group complain of vague pains in the hip aggravated by activity or by changes in the weather. He believes that such a common deformity rests on a postural basis and suggests that observations be carried out on these men in varying periods of physical training to determine whether symptoms are increased or whether the tilt corrects itself.

439 Lipscomb P R and Chatterton, C C Osteochondritis Juvenilis of Acetabulum *J Bone & Joint Surg* 24 372-381 (April) 1942

440 Milch, H Abduction Osteotometer, *J Bone & Joint Surg* 24 359-366 (April) 1942

441 Reed J and Sosman M C Gaucher's Disease *Radiology* 38 579-583 (May) 1942

442 Schein A J and Arkin, A M Hip Joint Involvement in Gaucher's Disease, *J Bone & Joint Surg* 24 396-410 (April) 1942

443 Zimmerman L E Tilted Pelvis *War Med* 2 465 (May) 1942

Caamaño⁴⁴⁴ reports 4 cases of traumatic dislocation of the hip in children aged 3½, 7, 10 and 13 years respectively. The function of the ischiocapsular ligament is discussed, and the dislocations are divided into two large groups, those with integrity of this ligament, or regular dislocations, and those in which the ligament has been destroyed, or irregular dislocations. In the regular dislocations one has to distinguish between posterior luxations and anterior luxations. In the irregular dislocations the following types are noted: (a) the anterior oblique dislocation of Bigelow, (b) the subpubic luxation (the head resting on the iliopectineal prominence), (c) the posterior and high dislocation known as the Monteggia type, (d) the perineal luxation, and (e) the sciatic luxation. The incidence of the various types of luxation is discussed, and it is pointed out that the posterior luxation is the most common. The 4 cases reported were of posterior iliac dislocations. Complications of traumatic dislocation of the hip are listed as follows: (1) retention of urine, particularly with pubic luxations, (2) partial fractures, (3) neural lesions, and (4) compression of the nerves, which may cause fatal reflex syncope. Treatment is outlined, and prognosis is discussed.

Allhoff⁴⁴⁵ presents a review of coxa vara and discusses constitutional deficiencies, trauma and accumulation of minor injuries as possible causes of the disease. Findings indicating a constitutional origin include bilateral involvement, familial incidence, appearance of the symptoms at the age of puberty and predominance of types with visible signs of endocrine disturbance. Caution is urged against making a diagnosis of epiphyseal separation, as this may lead to premature use of the limb.

The author reports 4 cases of coxa vara epiphysaria. In 3 cases pain in the hip or the knee had been complained of weeks or even months before the accident deemed responsible occurred. In 2 cases there resulted a complete separation of the head of the femur in the epiphysal line. In 1 case in which there was prompt treatment the progress of the disease was halted. In this case it was noted that the mother of the patient had limped since childhood. The roentgenogram taken of the mother showed a beveled-off femoral head with shortening and with varus position of the femoral neck. Endocrine disturbance was demonstrable in 2 cases.

XVII CONDITIONS INVOLVING THE ELBOW, FOREARM, WRIST AND HAND

PREPARED BY WAITER P. BLOUNT, M.D., MILWAUKEE

Developmental Anomalies—Persistence of the olecranon epiphysis in adults is described by O'Donoghue and Sell⁴⁴⁶. A case is reported in which attention was called to the condition by injury on one side. The lesion was found to be bilateral. The difference between this lesion and patella cubiti is restated according to Kohler. The true patella must be embryonic in origin, completely isolated, articulating and mobile.

Habbe⁴⁴⁷ reports 4 cases of patella cubiti in which the lesion is unilateral. The first 2 cases satisfy Kohler's other criteria. In the third case, trauma was the chief, if not the only, factor causing separation of the olecranon epiphysis in childhood. In the fourth case there was a definite trauma at 8 or 9 years of age associated with a "bump" on the elbow after that time. With a new injury fifteen years later

444 Caamaño, A. Traumatic Luxations in Children with Report of Cases, *Semana med* 1 1450-1457 (June 19) 1941

445 Allhoff, E. Etiology and Pathogenesis of Coxa Vara Epiphysaria, *Zentralbl f Chir* 68 1578-1581 (Aug 16) 1941

446 O'Donoghue, D. H., and Sell, I. S. Persistent Olecranon Epiphysis in Adults. *J Bone & Joint Surg* 24 940-941 (Oct) 1942

447 Habbe, I. E. Patella Cubiti. Report of Four Cases, *Am J Roentgenol* 48 513-526 (Oct) 1942

there were pain, weakness and swelling. Roentgen examination showed separation of the olecranon. The roentgenograms in this case were similar in appearance to those in the case of O'Donoghue and Sell.

[ED. NOTE—One cannot always clearly differentiate between a persistent epiphysis and an accessory bone of congenital origin on the one hand and an old traumatic separation of the epiphysis during childhood on the other. There is considerable medicolegal significance in the existence of an abnormal bone prior to trauma. In Habbe's first case, limited extension and pain gradually became disabling. One of us (W. P. B.) excised the accessory bone and reattached the triceps tendon to the ulna with complete restoration of function.]

A case of bilateral os epitriquetrum was discovered in the dissecting room by Saunders,⁴⁴⁸ and a study was made of this rare anomalous ossicle of the wrist. The larger bone had a maximum anteroposterior length of 6 mm. Both bones were wedged between the triquetrum, lunate, hamate and capitate bones. The accessory ossicles were attached to the palmar carpal ligaments. They were apparently congenital in origin.

Volkman's Ischemic Contracture—Foisie⁴⁴⁹ summarizes the growing conviction that ischemic contracture of the forearm has no essential connection with supracondylar fracture of the humerus or any specific injury. It is the result of ischemic infarction produced by segmentary arterial spasm of the main artery to the extremity with reflex spasm of the collateral circulation. In the resulting subtotal ischemia, the muscle bellies are most vulnerable and are first affected. The vasomotor activity is under the control of the sympathetic nervous system. In 30 cases from the literature in which an operation was performed, a stringlike constriction of the brachial artery about 2 cm. above its bifurcation was found at operation. The writer emphasizes the fact that spasm of this artery alone is not dangerous but that when combined with spasm of the collateral circulation it produces Volkmann's ischemia.

Treatment by ganglion block is recommended. If this fails, arterectomy of the constricted portion is preferable to periarterial sympathectomy, because it is easier to do and removes an artery which may be damaged and capable of continuous abnormal sensory stimuli.

Horwitz⁴⁵⁰ reports experimental work which disproves the suggested importance of venous obstruction in producing this syndrome.

[ED. NOTE—It is a clinical fact that with supracondylar fractures of the elbow in children dangerous arterial spasm is rare. Obliteration of the radial pulse is common. Faulty reduction, excessive flexion and tight bandaging may combine with swelling to impair the collateral circulation. Enthusiasm for periarterial sympathectomy must not blind one to the fact that ischemic contracture can usually be prevented by releasing constricting dressings, suspending the forearm with the elbow flexed to 90 degrees and applying external heat. If conservative measures fail prompt arterectomy should certainly be performed either with or without longitudinal division of the fascia of the forearm.]

Tendon Ruptures About the Elbow—A new case of avulsion of the biceps tendon is added to the literature by Hook and Mazet.⁴⁵¹ By repairing the injury

448 Saunders, R. I. de C. M. Os Epiphysium or Epitriquetrum, *Anat. Rec.* **84** 17-22 (Sept. 25) 1942.

449 Foisie, P. S. Volkmann's Ischemic Contracture. Analysis of Its Proximate Mechanism. *New England J. Med.* **226** 671-679 (April 23) 1942.

450 Horwitz, T. Significance of Venous Circulation About Elbow in Pathomechanics of Volkmann's Contracture. *Surg., Gynec. & Obst.* **74** 871-875 (April) 1942.

451 Hook, F. R. and Mazet, R. Jr. Avulsion of Biceps Tendon from Its Radial Insertion. Report of a Case. *U. S. Nav. M. Bull.* **40** 409-411 (April) 1942.

promptly, they were able to suture the tendon to the* radial tubercle with heavy silk. Recovery was prompt. Hamsa⁴⁵² reports a case of bilateral rupture in which surgical repair was refused. Seven months after the accident, slight weakness in supination and 25 per cent reduction in flexion were the chief disabilities. There was no pain.

[ED NOTE—Prompt operation has in past cases as well as in the present case enabled the surgeon to replace the tendon. Hamsa's observation suggests the advisability at times of conservative handling of the neglected injury.]

Coimbra and Andrade Faria⁴⁵³ report a case of partial rupture of the biceps tendon. Operative repair was not attempted.

Lesions of the Tendons—Tenosynovitis is reported from two army camps in England. Flowerdew and Bode⁴⁵⁴ observed 16 such cases in a few months. Twelve patients (out of 52 so employed) were men doing farm work to which they were unaccustomed. Of the 16 men, 14 did office or similar work before their enlistment. In all of the cases there was involvement of the extensor digitorum communis and in most cases also of the extensor carpi radialis longus. There was swelling and tenderness along the tendon with pain and crepitation on movement.

When an infantry division was put to harvesting grain, Pozner⁴⁵⁵ reported 7 men disabled with tenosynovitis, 4 partially disabled and 9 with mild symptoms. In both camps it was found that immediate complete rest was most effective. Prolonged disability and recurrence were noted if this was not enforced. Pozner suggests that strapping is more effective than splinting but says that plaster would be even better. Flowerdew and Bode asked the interesting question whether there is a similar occurrence of this condition in the nonmilitary population who have taken up unaccustomed manual labor.

Stewart⁴⁵⁶ reviews both traumatic and infectious tenosynovitis, with special interest in the phylogenetic development of the long head of the biceps.

Surgery of the Wrist—In the "Progress in Orthopedic Surgery for 1940" Ball's treatment of ganglion by the injection of a proteolytic enzyme (caroid) was noted. In February 1942, Key⁴⁵⁷ reported a case in which this treatment was carried out with disastrous results. Progressive subcutaneous necrosis over the dorsum of the wrist and forearm with a marked general reaction necessitated extensive debridement followed by a skin graft. There was permanent disability. The symptoms were believed to be due to contamination of the material with *Escherichia coli*, *Bacillus subtilis*, nonhemolytic streptococci and *Staphylococcus albus*, as well as to the chemical action of the enzyme. The writer warns against implantation or injection of such a substance unless it can be sterilized.

Anterior volar dislocation of the distal extremity of the ulna is reported by Cox⁴⁵⁸ following an automobile accident. Roentgenograms were reported to show

452 Hamsa, W. R. Bilateral Rupture of Biceps Brachii Lower Tendon, Nebraska M. J. 27:140 (April) 1942.

453 Coimbra, M. B., and Andrade Faria. Subcutaneous Rupture of the Biceps Brachii. New Case. Rev. brasil. de ortop. e traumatol. 3:111-115 (Nov.-Dec.) 1941.

454 Flowerdew, R. E., and Bode, O. B. Tenosynovitis in Untrained Farm Workers. Brit. M. J. 2:367 (Sept. 26) 1942.

455 Pozner, H. Report on Series of Cases of Simple Acute Tenosynovitis. J. Roy. Army M. Corps 78:142-144 (March) 1942.

456 Stewart, S. F. War Surgery and Traumatic Lesions. Traumatic and Infectious Tenosynovitis. Am. J. Surg. 56:43-48 (April) 1942.

457 Key, J. A. Treatment of Ganglion by Injection of Caroid, a Dangerous Procedure. J. A. M. A. 118:516-517 (Feb. 14) 1942.

458 Cox, F. J. Anterior Dislocation of Distal Extremity of Ulna. Report of Case. Surgery 12:41-45 (July) 1942.

nothing significant, and the disability was neglected for three weeks. At this time the correct diagnosis was made and an open reduction performed. The patient was left with some limitation of supination. The writer emphasizes the need for prompt reduction. The mechanism and the scanty literature are discussed.

[ED NOTE—One of us (W P B) performed such an open reduction for a clinic of three orthopedic surgeons who had never encountered this rare entity. The importance of early recognition and prompt open reduction cannot be over-emphasized. Contracture of the pronator quadratus muscle usually prevents closed reduction.]

Transplantation of the tendon of the flexor carpi ulnaris muscle is suggested by Green⁴⁵⁹ for the relief of pronation flexion deformity of the wrist. Through three incisions the flexor carpi ulnaris muscle is freed until a straight line may be developed to its insertion into the extensor carpi radialis tendon. With the hand in the corrected position, plaster is applied with the elbow flexed at a right angle, the forearm completely supinated and the hand in dorsiflexion. Guarded active exercises are started on the third day by bivalving the cast. The procedure was carried out in 15 cases of spastic paralysis, of which the results were excellent in 9, good in 4, fair in 1 and poor in 1. In 6 cases of obstetric paralysis the end result was excellent or good in 4, fair in 1 and poor in 1. The fair and poor results were apparently due to weakness of the transplanted muscles. In 2 cases of infantile paralysis, the results were excellent and good.

Abbott, Saunders and Bost⁴⁶⁰ described the anatomic implications and a carefully developed technic for arthrodesis of the wrist. Bone is removed from the crest of the ilium as the first step. In children, the incision through the periosteum is made along the lateral border of the crest, and the cartilaginous rim is displaced upward and medially to preserve it. Grafts are removed from the underlying bone with the osteotome held parallel to the margin. Under a pneumatic tourniquet the wrist joint is exposed through a curvilinear incision centering over Lister's tubercle on the dorsum of the radius. The dorsal carpal ligament and periosteum are incised longitudinally. The posterior ligament of the radial carpal joint is incised horizontally along the lower margin of the radius. With the wrist in palmar flexion, the cartilage is removed from the distal end of the radius and the contiguous surfaces of the navicular and lunate bones. The intercarpal and transverse intercarpal joints are exposed en masse by turning a curved flap distally with an osteotome. Thin sections of the cortex from the posterior surfaces of the navicular, lunate and capitate bones are left attached to their fibrous capsules and reflected. For the reception of the grafts, a flap is turned up proximally from the dorsal surface of the radius in adults. In children, a horizontal cut is made on the articular surface of the lower end of the radius. The cartilage is removed from the accessible surfaces of the navicular, lunate, capitate and lesser multangular bones. The spaces between the carpal bones and the lower end of the radius are packed with bone chips. Broad, pliable pieces of bone are then laid over the entire posterior aspect of the radiocarpal, intercarpal and transverse intercarpal joints. Fixation is secured by tucking the borders of the large grafts under the bases of the bone flaps and securing them by dorsiflexion. The inferior radioulnar and the carpometacarpal joint are not exposed. Plaster fixation extends from the tips of the fingers and thumb to the upper part of the arm with the elbow at right angles, the

⁴⁵⁹ Green W T. Tendon Transplantation of Flexor Carpi Ulnaris for Pronation Flexion Deformity of Wrist, *Surg, Gynec & Obst* 75 337-342 (Sept) 1942

⁴⁶⁰ Abbott L C, Saunders, J B de C M, and Bost, F C. Arthrodesis of Wrist with Use of Grafts of Cancellous Bone. *J Bone & Joint Surg* 24 883-898 (Oct) 1942

forearm in midprone position and the wrist in 10 to 15 degrees of dorsiflexion with the digital joints moderately flexed. After three weeks a short cast is substituted from just below the elbow to the metacarpophalangeal joints. Reports of 8 of 50 cases in which the operation was performed are offered in illustration of the method.

[ED NOTE—Fusion of the wrist joint is uncertain in outcome unless additional bone is used. For older children and adults, the distal end of the radius is a convenient source.]

Calcium Deposits—Cooper⁴⁶¹ has studied 8 cases of calcareous tendinitis in the metacarpal phalangeal region, and he reviews the subject of calcareous tendinitis in general. There was involvement once each of the first, second and fourth metacarpal phalangeal regions, and 5 times of the third. The patients' ages ranged from 38 to 60. There were 5 women and 3 men. The right hand was involved in every case. The microscopic section of material from 1 patient showed degenerated fibrous tissue with masses of amorphous calcium. The laboratory studies showed the uric acid to be within normal limits in 7 cases. The sedimentation rate was taken in 4 cases. It was 30, 26, 18 and 5 mm in these.

In each case the onset was acute. In 7 cases it occurred during the day. In no case was there recent trauma or acute illness. Pain, swelling and tenderness of the hand developed to a remarkable degree in a short time. Most of the patients were seen on the day of onset with diffuse swelling, local heat and redness strongly suggestive of an acute septic lesion.

Roentgenograms showed in each case a calcific deposit corresponding to the area of greatest tenderness. Some of the shadows seemed to follow the outline of the dorsal interossei muscles. In others, the conformation seemed to correspond to the distribution of the capsule. In 1 it appeared to be in the short flexor muscles of the thumb.

Examination revealed pronounced tenderness of a poorly defined nodule in the region of the deposit. Motion of the affected finger was extremely painful, especially extension of the metacarpal phalangeal joint with the finger flexed. Clinically the appearance was somewhat like that observed in uric acid gout, but the swelling was not of the tense, bluish type commonly seen in gout.

In 2 cases, exploration with a needle and the aspiration of a small mass of creamy calcific deposit did not seem to influence the course of the disease. No report is submitted on the case in which an operation was performed. Immobilization with plaster of paris or a splint extending to the finger tips was used with immediate relief. This immobilization was maintained for five to seven days. The acute symptoms subsided during this time in every case. Slight or moderate residual tenderness which lasted for several weeks was treated with diathermy through the clasped hand. During the course of treatment the calcific deposits grew rapidly less apparent in roentgenograms. They were absent or very small in every case at the end of 1 month.

As in calcareous tendinitis elsewhere, the cause remained obscure and the calcium deposit was undoubtedly present long before the development of symptoms. The mechanism which precipitated the acute symptoms was not evident. The occurrence in the right hand in the reported cases suggests the likelihood of trauma of use as a contributing factor.

Different but interesting are 3 cases of interstitial calcinosis. In 2 the tip of a finger was involved and in 1 the right fourth toe. It is remarkable that in all of these

⁴⁶¹ Cooper W. Calcareous Tendinitis in Metacarpophalangeal Region. *J Bone & Joint Surg* 24:114-122 (Jan) 1942.

3 cases, reported by Bereow and Poppel,⁴⁶² the calcinosis was associated with scleroderma and Raynaud's disease. The writer thought that Raynaud's disease might predispose to both of the other lesions, although he realized that any of the three lesions might appear independently.

Surgery of the Hand—In his usual masterly fashion, Bunnell⁴⁶³ prefaces a new article with a demonstration of the primordial character of the intrinsic muscles of the hand. He shows that the hand developed phylogenetically before the arm since these muscles are present in the early fish and well developed in the amphibia. From dissection of fresh cadavers he describes the dorsal aponeurosis, or extensor assembly, which permits the coordination in action of the long extensors and flexors and the lumbricalis and interosseus muscles. The conjoined tendons of the interosseus and lumbricalis muscles may either flex the proximal finger joint or extend the distal two finger joints, according to whether the aponeurotic sleeve shifts distally or proximally. The transverse fibers over the back of the proximal phalanx can be made to shift on the phalanx longitudinally 15 mm, although in ordinary use they shift only 7 mm, while the narrow ventral band which is blended with the joint capsule shifts only 3 mm. When the sleeve is distalward down back of the phalanx, the intrinsic muscles can flex the proximal finger joint, but when the sleeve is drawn proximally by the action of the long extensor tendon and the sleeve is over the joint, a sort of "shifting of gears" takes place, and the proximal joint is stabilized in extension and the intrinsic muscles extend the distal two finger joints or impart lateral motion. The intrinsic muscles flex the proximal joint only when the long extensors relax. The functional anatomy of the other intrinsic muscles is thoroughly discussed. Clinical types of injury of intrinsic muscles are then described, with an appropriate repair for each injury. Removable wire sutures are ingeniously used, as outlined in "Progress in Orthopedic Surgery for 1941."

Miller⁴⁶⁴ presents an end result study of 300 cases of tendon injury of the hand and wrist in 136 of which there was a complete follow-up. His conclusions are:

- 1 Functional results are poorest in lacerations occurring over the proximal phalanges and middle phalanges.

- 2 Lacerations of flexor tendons occurring at the wrist and over the palm generally heal with good functional results.

- 3 Lacerations of the extensor tendons regardless of their location heal without functional disability in 92 per cent of the cases.

After 4 plastic operations on digital flexor tendons Pinkerton⁴⁶⁵ surrounded the tendon with amnioplastin. It was his impression that the function of the tendons was improved by this procedure. The results were satisfactory as long as three months after operation. He suggested the use of amnioplastin after suturing cut flexor tendons. His membrane was prepared from human amnion by the pathology laboratory according to the method of Penfield.⁴⁶⁶

⁴⁶² Bereow, C. and Poppel, M. H. Interstitial Calcinosis Circumscripta Associated with Scleroderma and Raynaud's Disease. *Radiology* **39** 96-98 (July) 1942.

⁴⁶³ Bunnell, S. Surgery of Intrinsic Muscles of Hand Other than Those Producing Opposition of the Thumb. *J. Bone & Joint Surg.* **24** 1-31 (Jan) 1942.

⁴⁶⁴ Miller, H. Repair of Severed Tendons of Hand and Wrist. Statistical Analysis of Three Hundred Cases. *Surg. Gynec. & Obst.* **75** 693-698 (Dec) 1942.

⁴⁶⁵ Pinkerton, M. C. A Amnioplastin for Adherent Digital Flexor Tendons. *Insect* **1** 70-72 (Jan 17) 1942.

⁴⁶⁶ Penfield, W. Amnioplastin. A Warning. *Brit. M. J.* **2** 668 (Nov 16) 1940.

Disturbed by the limited independent extension of the fourth finger of his own right hand, Batty-Smith⁴⁶⁷ submitted to an operation to remove the fibrous bands between the extensor tendons of the third, fourth and fifth digits. These proved to be transverse rather than oblique. There is evidently considerable variation in their direction. At the first operation, the bands connecting the extensor tendons of the fourth finger were cut. No improvement in extension of the digit was obtained. Five years later a second operation was performed, with the patient under local anesthesia and able to cooperate. The extensor tendons of the fourth and fifth fingers were identified. It was found that extension of the ring finger caused tightening of the slip of the extensor communis to the fifth. Extension of the little finger alone was performed entirely by the extensor digiti quinti proprius. Attempts to extend the fourth finger alone were futile while the little finger was held flexed. Therefore, about 1 inch (2.5 cm) of the slip of the extensor communis to the fifth finger was excised, only the extensor digiti quinti being left to this finger. Simple exercises were begun on the twelfth day. Emphasis was placed on flexing the little finger while extending the ring finger. A maximum improvement of function was obtained in the first three weeks. The operation was a complete success in that the fourth finger could be lifted $\frac{3}{8}$ inch (1.6 cm) independently and that this finger could be straightened to within 25 degrees of complete extension while the little finger was held flexed in the palm. The writer concludes that the tendinous slips are not important factors in disability of the ring finger. For persons who require independent extension of the fourth finger, as in piano playing, this simple operation is advised.

Finger Amputation—Traumatic amputation of a finger tip is a frequent accident, particularly in the tank corps. In most cases the tip of the middle finger is involved but injury of each of the digits has been noted. In the majority of the cases, the base of the nail is not completely avulsed. Terhune and Camp,⁴⁶⁸ from Camp Polk, La., suggest primary debridement with a split thickness skin graft applied to the raw surface. Bleeding is first carefully controlled and sulfanilamide powder sifted on the stump. In 6 of 8 cases the graft took well. The writers prefer the method to reamputation at the distal interphalangeal joint. The injury is treated by DeJongh⁴⁶⁹ by sliding a flap of skin from the palmar margin of the wound over the tip of the finger. With the area under block anesthesia with procaine hydrochloride the distal end of the phalanx is trimmed and then a transverse incision is made on the palmar surface $\frac{3}{16}$ to $\frac{1}{4}$ inch (0.5 to 0.6 cm) proximal and parallel to the edge of the amputation. The incision is extended from a midlateral point on one side to the same point on the other side and carried down through the layers of the skin and just to the areolar tissue. No undercutting is necessary. The freed section is moved distally and dorsally until it covers the end of the finger and is held in place with three sutures passed through the nail or its bed and through the distal edge of the skin flap. The denuded area proximal to the section of skin is allowed to granulate in. No difficulty has been noted with the resulting scar. Twenty-eight cases are reported with only 1 possible failure. Good cosmetic and functional results are claimed.

467 Batty-Smith, C. G. Operation for Increasing Range of Independent Extension of Ring Finger for Pianists, *Brit J Surg* **29** 397-400 (April) 1942.

468 Terhune, S. R., and Camp, M. N. Traumatic Amputation of Finger Tips. *South Surgeon* **11** 646-651 (Sept.) 1942.

469 DeJongh, E. Simple Plastic Procedure of Fingers for Conserving Bone Tissue and Forming Soft Tissue Pad. *Am J Surg* **57** 346-347 (Aug.) 1942.

Jones⁴⁷⁰ reports 18 cases from the United States Marine Hospital in San Francisco in which the involved finger was flexed in the palm, where the defect was covered by a flap graft from the thenar or hypothenar surface with the base directed proximally. The flap was sutured to the skin or the nail on the dorsum and the sides of the graft were sutured to the sides of the defect as far proximally as possible without tension or kinking. The finger was held in position for fourteen to eighteen days with adhesive plaster until the graft was cut loose. The writer recommends the method because the graft of the palmar skin and subcutaneous tissue more nearly approximates the normal appearance and texture.

Correction of Opponens Paralysis—Irwin⁴⁷¹ reviews the indications for and technic of the basic transplant of the flexor sublimis tendon of the fourth finger to the proximal phalanx of the thumb. He emphasizes the following features:

- 1 The course of the transplanted tendon from the muscle belly to the pulley must be in a straight line.

- 2 A pulley is constructed by passing the transplant under and over the flexor carpi ulnaris tendon and maintaining it in position by a hitch from a portion of the flexor ulnaris tendon.

- 3 The pulley must allow free gliding motion of the tendon by presenting its smooth, glistening surface to the inside and being one-third larger than the diameter of the tendon.

- 4 The tendon must lie in front or toward the flexor side of the metacarpophalangeal joint at the base of the proximal phalanx.

- 5 The tendon is fastened directly into the bone entering the proximal phalanx on the border adjacent to the web.

The palmaris longus tendon is never removed from its normal site to furnish motor power to the transplant. It normally takes part in opposition. In the presence of an arthrodesed wrist, the flexor ulnaris or radialis tendon may be used to reenforce the basic transplant. The secondary tendon must be attached to the tendon of the basic transplant proximal to the pulley. The operative technic and after-care are thoroughly discussed.

T. C. Thompson⁴⁷² uses the flexor sublimis tendon of the ring finger without pulling it from its canal. The tendon is severed at the base of the fourth finger and drawn out through a longitudinal incision in the palm just to the radial side of the hypothenar eminence. It is then drawn subcutaneously across the center of the thenar eminence to the distal end of the first metacarpal bone and the base of the proximal phalanx of the thumb. The lower border of the transverse carpal ligament thus forms a pulley at some distance from the base of the thumb. The action in adduction and especially in rotation of the thumb is much more efficient than when the tendon was brought out above the wrist instead of distally to the sheath of the flexor pollicis longus muscle.

A hole is drilled through the distal end of the first metacarpal so that half of the tendon enters this bone just to the radial side of the extensor pollicis longus. The other half of the tendon is then brought around the dorsal surface of the thumb superficial to the extensor pollicis brevis and extensor pollicis longus tendons, and

470 Jones R. A. Method for Closing Traumatic Defect of Finger Tip. *Am J Surg* 55 326-338 (Feb.) 1942.

471 Irwin, C. E. Transplants to Thumb to Restore Function of Opposition. *End Results, South M J* 35 257-262 (March) 1942.

472 Thompson, T. C. Modified Operation for Opponens Paralysis. *J Bone & Joint Surg* 24 632-640 (July) 1942.

drawn through a small tunnel in the fascia and periosteum at the base of the proximal phalanx. The two ends of the transplanted sublimis tendon are then sutured together.

To maintain a functional position of the thumb in selected cases in which there is too extensive paralysis to permit the foregoing operations, C F Thompson⁴⁷³ proposes stabilization of the first metacarpocarpal joint by placing a bone graft between the first and second metacarpals. He uses the operation also in maintaining the spastic thumb away from the palm.

The first interosseous space is exposed through a dorsal longitudinal incision. The radial artery is isolated. The first dorsal interosseous muscle is split and preserved to cover the dorsal aspect of the graft. The adductor pollicis muscle or its remnant forms the floor of the graft bed. Holes are placed in the adjacent cortices of the first two metacarpals to receive the 1 cm spikes of bone on each end of the graft. The distance between the bone recesses in the metacarpals is measured with the thumb in extreme opposition. A block of bone is removed from the tibia and shaped to fit with a spike on each end. Tension of the tissues holds the graft firmly in position. A plaster cast so molded as to support the space between the index finger and the thumb is worn for twelve weeks.

Of the 7 operations performed, only 1 resulted in failure. A pseudarthrosis occurred between the graft and the first metacarpal bone.

Dupuytren's Contracture —The perennial discussion of Dupuytren's contracture is continued by Lund,⁴⁷⁴ who finds that the deformity is more prevalent among patients with epilepsy than among other persons. A colony of 190 male and 171 female epileptic patients treated with phenobarbital was examined for localized fibroplasias. Fifty per cent of the males showed no change in the palm, 22.6 per cent had nodules or thickened bands in the palmar fascia, an additional 15.8 per cent had the characteristic puckering of the skin in the palm, and 11.6 per cent had contractures of the fingers. The various deformities were about half as frequent in females. In addition, 13 males and 12 females had fibroma plantae. There were 12 cases of periarthrosis humeri. Of 100 males examined, 29 had subcutaneous fibromas of the dorsal aspect of the middle joints of the fingers and 3 had induratio penis plastica. Of 100 females examined, 13 had subcutaneous fibromas of the fingers. Dupuytren's contracture was present in most of the cases in which there were other manifestations of localized fibroplasia.

Examination of a control group of 1,021 brewery workers showed that Dupuytren's contracture was four times as frequent among the epileptic patients as among the workers and that the age of onset was lower among the former. No definite correlation was found between the incidence of Dupuytren's contracture and the age of onset of the epilepsy, the frequency of seizures or the size of the dose of phenobarbital. Three questions are suggested which need further investigation.

1 Is there any hereditary connection between epilepsy and a fibroplastic diathesis?

2 Are these localized fibroplasias due to functional disturbance of the vasomotor system of persons with epilepsy (constant hypersympatheticotony or universal tonus storm at each epileptic paroxysm)?

3 Can protracted therapy with phenobarbital be responsible for the high incidence of localized fibroplasia among persons with epilepsy?

⁴⁷³ Thompson, C F. Fusion of Metacarpals of Thumb and Index Finger to Maintain Functional Position of Thumb, *J Bone & Joint Surg* **24** 907-911 (Oct.) 1942.

⁴⁷⁴ Lund, M. Dupuytren's Contracture and Epilepsy, *Acta psychiat et neurol* **16** 465-492, 1941.

The entire subject of Dupuytren's contracture has been thoroughly restudied by Horwitz⁴⁷⁵ on the basis of (1) the dissection of the palmar fascia in 60 hands presenting no gross abnormality, (2) the microscopic anatomy of the palmar fascia in 27 normal hands and (3) the structure of the tissue removed in 35 cases of Dupuytren's contracture. He concludes that previous considerations of such etiologic factors as trauma, chronic specific or nonspecific inflammatory processes, circulatory stasis, focal infections, gout, diabetes mellitus, arthritis, embryonic malformations, peripheral or central neurologic disturbances and endocrinopathies have been founded on wholly inadequate evidence and are substantiated neither by a critical analysis of the clinical and histologic material in his investigation nor by the data reported by other writers. He does conclude that the essential process is a benign fibroplasia of the palmar connective tissues with histologic features and clinical behavior resembling those of other localized fibroplasias. Such factors as heredity, senility and a fibroplastic diathesis appear to have etiologic significance.

Widespread surgical excision of the involved tissues is considered essential for permanent correction of the deformity. Not only should the contracted superficial palmar fascia and its digitations be removed, but also the attachments to the skin, the paratendinous septums and even the distal portions of the deep interosseous fascia. When the correction of deformities of the fingers necessitates wide excision and division of soft tissue or resection of bone, immediate amputation is sometimes to be preferred. Adams⁴⁷⁶ suggests the simple transverse incision without the addition of a connecting longitudinal incision for fear of necrosis of the skin flap.

XVIII RESEARCH

PREPARED BY ARTHUR STEINDLER, M.D., AND THE STAFF OF CHILDREN'S HOSPITAL, IOWA CITY

Classification—Brailsford⁴⁷⁷ studied the roentgenograms of a full term fetus at birth. No ossified nuclei of epiphyses are present, except one for the epiphysis of the lower end of each femur and sometimes a smaller one for the head of the tibia and the head of the humerus.

The ossification of the diaphyses appears to be uniform throughout. The nutrient foramina can be made out in the long bones. The extremities of the diaphyses are already defined and regular in outline.

As the cartilage of the epiphyses does not show at the joints, there appear to be wide gaps between the extremities of the long bones. The nuclei for the os calcis and astragalus are large and beginning to show evidence of their shape. A small nucleus for the cuboid may also be present. In the wrist a small nucleus for the os magnum may be the only indication of ossification of the carpus.

The author then describes in detail the roentgenographic appearance of the skull, spine and pelvis. He also discusses different anomalies and intrauterine injuries from the point of view of the roentgenologist.

[ED. NOTE—For the study of the intrauterine roentgen interpretation of many anomalies, injuries and diseases, this article is to be recommended.]

475 Horwitz, T. Dupuytren's Contracture. Consideration of Anatomy of Fibrous Structures of Hand in Relation to This Condition with Interpretation of Histology, *Arch. Surg.* 44: 687-706 (April) 1942.

476 Adams, H. D. Dupuytren's Contracture. *S. Clin. North America* 22: 899-906 (June) 1942.

477 Brailsford, J. F. Skeleton at Birth. *Brit. J. Radiol.* 15: 213-223 (Aug.) 1942.

Robinow⁴⁷⁸ studied the ossification centers of 31 children. The ages were determined at which nineteen centers appeared in the group. These data were intercorrelated and subjected to a factor analysis.

The analysis yielded three factors: a "round base" factor, an "epiphysis" factor, and a factor having no obvious meaning, probably an artefact.

An appreciation of the first two factors helps one to understand certain cases in which skeletal development is atypical. Methods are suggested by which meaningful "skeletal ages" may be assigned in such cases.

There was found in 2 boys and 2 girls of one family an acceleration of the development of round bones associated with general acceleration of skeletal development.

Buehl and Pyle⁴⁷⁹ report on the ossification of three centers:

1. The distal epiphysis of the ulna is normally the last epiphysis of the wrist to calcify and its calcification begins between the ages of 5 and 7, depending on the sex and rate of development.

2. The first sesamoid bone of the thumb begins to calcify before adolescent changes begin and consequently is useful as a predictor of the menarche.

3. The crest of the ilium begins to ossify at the ages of 12 and 13½ years respectively in boys and girls. These three centers were studied, and the age at which ossification began was found to be 5½, 10 and 13 years respectively for girls and 7½, 12 and 14 years for boys.

Ossification began in these three centers according to the normal order of general development peculiar to each sex, i. e., boys follow girls in sequence of ossification.

Ossification began in the crest of the ilium within six months of the menarche in two thirds of the girls.

It is suggested that ossification of the crest of the ilium might possibly indicate a point in the maturation cycle of the male which is comparable to that existing in the female at the time of menarche.

Endocrines—In previous experimental work the Silberbergs⁴⁸⁰ used acid extracts of the anterior lobe of the hypophysis in growing mice and guinea pigs and noted temporary stimulation of the proliferation of epiphyseal cartilage followed by a premature aging process of the skeletal tissues.

However, several investigators pointed out that the anterior lobe of the hypophysis contains a growth-promoting substance that can be extracted by alkaline but not by acid solutions. The authors consequently decided to compare the effects of alkaline extracts (antuitrin G) with the results obtained with acid extract. Forty-three mice and 8 guinea pigs were used. One group of mice consisted of growing animals 5 to 6 weeks old, the other, of adults 3 to 4 months old. The first group received 0.1 cc. of the alkaline extract three times weekly for one, two and four weeks and two and three months. The other group received 0.15 cc. three times weekly for one, two and four weeks. Controls were maintained in all experiments. Two guinea pigs received 1 cc. of the extract intraperitoneally daily for four days, and 2 others received the same dose for fourteen days.

478 Robinow, M. Appearance of Ossification Centers. Groupings Obtained from Factor Analysis, *Am J Dis Child* **64** 229-236 (Aug) 1942.

479 Buehl, C. C., and Pyle, S. I. Use of Age at First Appearance of Three Ossification Centers in Determining Skeletal Status of Children, *J Pediat* **21** 335-343 (Sept) 1942.

480 Silberberg, M., and Silberberg, R. Effects of "Growth Hormone" of Anterior Hypophysis (Antuitrin G) on Skeleton of Mice and Guinea Pigs. *Am J Path* **18** 1141-1157 (Nov) 1942.

The authors state that the effects observed with this alkaline anterior pituitary extract are in principle the same as those observed when the acid anterior hypophyseal extract was used. In growing mice and guinea pigs the former extract influences all three phases of skeletal development and aging. It promotes processes of bone formation as well as those of resorption of bone. In adult mice which have reached the end of physiologic growth it does not renew epiphyseal cartilage proliferation.

Sutro and Pomerantz⁴⁸¹ report an experimental study of the effect of estradiol benzoate on bone growth in young dogs, particularly as contrasted to the findings with mice.

Eight mongrel dogs were used, of which 3 served as controls and 5 (3 females and 2 males) were used experimentally. Weekly injections of estradiol benzoate were given for a period of five to seven and a half months. Roentgenographic and microscopic studies of the bones were made. The following areas were studied: costochondral junction, humeroscapular articulation, knee, hip, pubic symphysis, sacroiliac articulation, calvarium and lumbar vertebrae. Some of the nonosseous tissues were also examined microscopically.

At the end of the experiment, the only epiphyseal plate still partially open in the long bones was that in the upper end of the humerus, whereas in the controls the epiphyseal plates at the upper end of the humerus, tibia and femur were open. The heights of the vertebral bodies and the sternum were shorter in the experimental animals. In addition, all the long bones of these animals presented some narrowing proportional to the stunting of longitudinal growth. In contrast to what is found in mice, no evidence of osteosclerosis was observed in either the metaphyseal or the endosteal regions; furthermore, the density of the calvarium was unaffected. As for the pubic symphysis, the lowermost portion was merely smaller than in the control dogs. The sacroiliac region showed no change. In the experimental animals, the penis showed only a small proximal segment of bone, while in the control animals it had a long stem of bone running throughout its length.

Microscopic observations confirmed the roentgenographic findings. They showed plainly that the epiphyseal plates of the examined long bones of the experimental animals were closed. The costochondral junctions and the growth plates in the pubic symphysis were found only slightly affected, in that the number of hypertrophic cells was diminished. The articular cartilages of the long bones were slightly thinner and contained fewer cells in the experimental animals than in the controls. There was no premature fibrillation or degeneration of the cartilage matrix, and no osteosclerosis was noted in the metaphyseal or the endosteal areas. The bones and ligaments comprising the pubic symphysis and the sacroiliac articulations were unaffected.

In summary the authors conclude that the prolonged administration of estradiol benzoate to young mongrel dogs did not cause osteosclerosis, although inhibition of the growth of the skeleton and disturbance of the development of bone in the penis did occur. These findings are unlike those encountered in mice, in which not only stunting of growth but osteosclerosis has been observed. The absence of osteosclerosis in the dogs suggests that other factors besides the inhibition of growth may be responsible for the excess production of bone in certain animals after the administration of estrogen.

⁴⁸¹ Sutro C J, and Pomerantz, L. Changes in Osseous Tissues of Young Dogs After Prolonged Administration of Estradiol Benzoate (Estrogen), *Arch Path* 33 305-311 (March) 1942

Biemei⁴⁸² reports on the probable causes of the subepiphyseal resorption of the surface of the diaphysis of long bones which is responsible for the shaping of the bones. He describes the histologic picture of the processes and refers to his previous paper in which he describes a similar process taking place in the condition known as osteitis fibrosa. He then points out that the parathyroid gland is "ill adapted" to be considered even by implication as a regulator of resorption and deposition of bone by its regulation of calcium storage in bone.

On the other hand, estrone has been shown experimentally to cause osteitis fibrosa, consequently the author used this substance in rats and observed an increase in the normal erosion at the surface of the bone. He also points out that Gordon and Pfeiffer in 1938 showed that the effects of estrone can be suppressed by testosterone. Since estrone was considered normally present, testosterone was given to normal rats by the author, and a consequent reduction in erosion was noted. Consequently, the author feels that it is an estrone-testosterone ratio that acts as a regulator rather than parathyroid hormone.

As to an explanation of the choice of specific locations of areas of bone resorption the author offers the suggestion that it occurs in the subepiphyseal region because of the thin-walled veins that exist here, making this area more permeable for hormonal activity.

The author also points out that one fairly dependable characteristic of female bones is the greater depth of the osseous fossa in the female than in the male. He attributes this to presumable preponderance of estrogens in the female.

Cartilage—A new histochemical method for studying the cytoplasm of cells is described by Hass,⁴⁸³ which consists of a microscopic interreaction in the presence of nitrous acid between a particular product derived from crystal violet and an unknown cytoplasmic component which is especially abundant in the region of the cytoplasmic membrane. Several types of cells were studied, but it was found that only cartilage cells possess this component in reactive form. Even cartilage cells differ in degree of reactivity in accordance with the type and stage of differentiation. In infantile cartilage, the capacity to react is acquired by the cytoplasm as the cells differentiate from the perichondrium. It increases as the cells become embedded in a matrix but decreases as the cells undergo decay at the zones of ossification. The cells of infantile epiphyseal cartilage varied with their stage of differentiation. The undifferentiated cells of perichondrium and neighboring fibrocytes did not react.

Cells of costal and patellar cartilage gave the same type of reaction, though of a lower order.

Cells of hyaline cartilage of vertebral bodies gave a positive reaction. A similar reaction was possessed by the fibrocartilaginous part of the intervertebral disk.

Cells of the elastic cartilage of the auricle of the ear gave a positive reaction but of a lower order of reactivity.

A low order of reactivity was also characteristic of most cells of the geniculate semilunar cartilage. Cells which gave a strongly positive reaction were surrounded by a hyaline matrix.

482 Bremer, J. L. Influence of Estrogens on Shape of Long Bones, *J. Bone & Joint Surg.* **24** 32-37 (Jan.) 1942.

483 Hass, G. M. Studies of Cartilage. New Histochemical Reaction with High Specificity for Cartilage Cells, *Arch. Path.* **33** 174-181 (Feb.) 1942.

The formation of new cartilage was observed by the Clarks⁴⁸⁴ microscopically in the living animal by means of "round table" chambers permanently installed in the ears of rabbits. The installation involves the cutting of a hole 0.6 mm in diameter clear through the ear and the insertion of a double-walled chamber with a transparent observation space. Thus all the tissue which appears in the space over the table is newly formed and the cytologic details of its growth and differentiation can be followed by microscopic observation over a period of months.

In contrast to the behavior of blood vessels and connective tissue cells, which promptly invaded the table space from the periphery in every case, and to that of the lymphatics, which usually grew in, and of the nerves, which frequently regenerated, the new formation of cartilage was much slower, more sporadic and more restricted in amount. Cartilage formation occurred in 10 of 23 round table chambers studied intensively for from four to twenty months.

Cartilage appeared relatively late, in most cases after the vascularization of the table area was complete. It formed in regions of slow or moderate circulation and did not take place under the conditions of mild inflammation which favored the rapid growth of other tissues.

After a few weeks of slow increase the new cartilage usually became stationary and remained unchanged for several months, while in a number of cases it receded and occasionally it disappeared.

Cartilage formation was seen to occur in some cases near the edge of the table in continuity with the cut edge of the preformed cartilage and with others well out in the table area in the midst of the new tissue. The regions of new formation were restricted in number, occurring at one to at most three points only, and the amount formed was relatively small.

The new cartilage arose from elongated motile cells, containing characteristic uniformly disturbed granules, which became stationary and spherical, after which the granules enlarged and coalesced to form the large fat droplets similar to, although rarely as large as, those seen in the original ear cartilage. At the same time, a clear homogeneous substance (matrix) appeared between the cells. A number of neighboring cells underwent these changes simultaneously. In succeeding weeks other elongated cells around the edges of the new cartilage frequently underwent this transformation, thereby increasing the cartilage mass.

Mitotic division of the new cells was not observed. The question as to whether the wandering cells which transformed into cartilage were specific cells, derived from the original cartilage or perichondrium, or whether they were ordinary fibroblasts, originating from connective tissue cells, was not settled.

Spontaneous development of bone in the midst of newly formed cartilage occurred occasionally, and in 1 instance it was possible to study the cytologic details of bone formation in living tissue. The cartilage developed in the interstices of circulating vascular networks, and after the formation of the intercellular matrix the blood vessels in the vicinity retracted and the cartilage became non-vascular. The new bone first appeared in areas of nonvascular newly formed cartilage and invaded the bone. Growth and resorption of bone were subsequently seen to occur simultaneously with no further alteration in the supplying blood vessels.

⁴⁸⁴ Clark E. R. and Clark E. L. Microscopic Observations on New Formation of Cartilage and Bone (in Transparent Chambers in Ear) in Living Mammal. *Am J Anat* 70: 167-200 (March) 1942.

It has been previously shown experimentally by Rosenthal, Bowie and Wagone⁴⁸⁵ that the respiratory power of the cartilage cell declines with advancing age, while the glycolytic power does not change. Because of this decline the authors present a study of the nature and capacity of the respiratory enzymes of bovine cartilage.

Functionally, the respiratory system in cells can be divided into two parts (a) a substrate-activating (dehydrogenatic) component and (b) an oxygen-activating component. These investigations were based on the first part, i.e., the substrate-activating component. Aerobic methylene blue technic was used for the estimation of the dehydrogenatic capability of the surviving cartilage slices.

Dextrose and mannose were the most effective substrates for the dehydrogenatic process.

The paper presents experimental data to show that the dehydrogenatic power of bovine articular cartilage is qualitatively and quantitatively greater than that reported in previous experiments.

They give a reason for the fact that other investigators have not detected a marked dehydrogenatic activity in articular cartilage toward readily oxidizable metabolites, in that they used either damaged or aged cartilage.

Evidence is presented by the Gutmans⁴⁸⁶ that a phosphorylative glycogenolytic enzyme is present in calcifying cartilage which is capable of synthesizing potential substrates for bone phosphatase at zones of calcification before blood sources become available, and of supplementing those blood sources after they become available. Inorganic phosphate for calcification can be formed from organic esters not only by bone phosphatase but by phosphorylase.

Experiments were performed with tissue pulp made from the proximal and distal ends of the femurs, tibias and humeri of young rabbits or rats. The effects of young rabbits' livers and epiphyseal pulp on the inorganic phosphorus content of phosphate-glycogen mixtures and the influence of temperature and fluoride on the reaction were determined. Also the effects of aqueous extracts of young rabbit epiphyses on the inorganic phosphorus content of phosphate-glycogen mixtures with and without added muscle adenylic acid, and on glucose-1-phosphate, are presented. The results imply a rapid rate of reaction of the enzymes involved which contrasts with the extremely slow reverse catalytic effect of bone phosphatase. Activation of adenylic acid further indicates that the results cannot be ascribed wholly to bone phosphatase.

The aim of this work by Hass and Garthwaite⁴⁸⁷ is to obtain positive data about the composition of the cartilage. They divided the methods of study in five parts: (1) preparation of cartilage, (2) extraction of the prepared material, (3) hydrolysis of the extracted tissue, (4) determination of the quantity of reducing substances in the hydrolysis, and (5) determination of the quantity of sulfate in the hydrolysis.

They worked on fresh epiphyseal cartilage obtained from infants and cut with a freezing microtome.

From averages of the numerical data they concluded that chondroitin-sulfuric acid comprises about 20 per cent of the dry weight. Of this amount, a small

⁴⁸⁵ Rosenthal, O., Bowie, M. A. and Wagone, G. Nature of Dehydrogenatic Ability of Bovine Articular Cartilage. *J. Cell & Comp. Physiol.* **19**: 15-288 (Feb. 20) 1942.

⁴⁸⁶ Gutman, A. B. and Gutman, E. B. Phosphorylase in Calcifying Cartilage. *Proc. Soc. Exper. Biol. & Med.* **48**: 687-691 (Dec.) 1941.

⁴⁸⁷ Hass, G. M., and Garthwaite, B. Studies of Cartilage. Some Effects of Mediums of Different pH Values on Composition of Cartilage. *Arch. Path.* **33**: 145-162 (Feb.) 1942.

fraction was extracted with neutral 10 per cent aqueous solution of calcium chloride and a large fraction was extracted at p_H 11, while complete extraction in the range p_H 4 to 12 was possible only at p_H 12

Sulfonamide Compounds—For one year Bick and Pheasant⁴⁸⁸ observed the results of implantation of sulfonamide compounds when implanted in the soft tissues

The following conclusions were drawn. As long as small amounts of the drug were used and also as long as the drug was implanted deeply, that is, below the subcutaneous tissues, neither delay in healing nor delay in recovery of function of the joint was noted. Small doses were adequate for the control of infection. Small doses do not cause reactions, such as adhesions, fibrosis or other alterations in the joint. Apparently sulfathiazole and sulfanilamide have equal protective powers, with sulfanilamide the easier to apply.

[ED NOTE—These conclusions confirm the observations now being made in hospitals of the armed forces all over the world.]

⁴⁸⁸ Bick, E. M., and Pheasant, H. C. Local Application of Sulfonamides to Synovial Surfaces, *J. Bone & Joint Surg.* **24**: 937-939 (Oct.) 1942

VITAMIN B₁ NUTRITION IN SURGICAL PATIENTS AS DETERMINED BY THE BLOOD LEVEL OF PYRUVIC ACID

I HEPATIC DISEASE

HARRY A DAVIS, M.D., AND FRANZ K BAUER, M.D.

NEW ORLEANS

Carboxylase is an enzyme which catalyzes the decarboxylation of pyruvic acid to carbon dioxide and water. It was first recognized by Neuberg and Karczag¹. Auhagen² showed that the activity of carboxylase is dependent on the presence of a coenzyme which is known as co-carboxylase and which is found in animal tissues. Later Lohmann and Schuster³ were able to isolate cocarboxylase and to demonstrate that it is a pyrophosphoric ester of vitamin B₁ (thiamine). Vitamin B₁ (thiamine) after ingestion is absorbed from the intestine by diffusion into the blood stream. It reaches the liver and the kidneys, where phosphorylation takes place and where the thiamine is stored as cocarboxylase, or diphosphothiamine (Ochoa and Peters⁴, Westenbrink and Goudsmit⁵). Dephosphorylation of the diphosphothiamine may take place in all of the tissues but appears to be carried out mainly in the liver and the kidneys (Ochoa⁶, Tauber⁷). Dephosphorylation results in the formation of free thiamine. This may be released into the blood stream, after which it is

rephosphorylated by other tissues, or it may be excreted in the urine. It is thus evident that vitamin B₁ (thiamine) after absorption exists in two forms in the animal body either as free thiamine or as diphosphothiamine, most of it occurring in the latter form. Peters⁸ demonstrated that thiamine is essential in the metabolism of pyruvic acid. Since pyruvic acid is a degradation product of carbohydrate metabolism, the importance of thiamine can be readily appreciated. It should be remembered, however, that free thiamine is inactive and that it is only diphosphothiamine which is capable of oxidizing pyruvic acid to carbon dioxide and water. Since the liver is an important storage depot for the active form of thiamine, namely diphosphothiamine, several interesting questions present themselves. What is the effect of thiamine on function of the liver, and what are the effects of diminished hepatic function on the physiologic availability of thiamine? In this regard certain observations are of interest. Tonutti and Wallraff⁹ have shown that the livers of B₁-deficient mice are lacking in glycogen. This they said was due not to inanition but to inability of the livers of such mice to store glycogen. Similar observations were made by Heimann¹⁰ in rats. Longenecker and his co-workers¹¹ found a diminution of fat in the livers of thiamine-deficient rats. The administration of thiamine to such rats caused an increase in the amount of fat in the liver. The purpose of the present study was to determine (1) the inci-

From the Department of Surgery of the Louisiana State University School of Medicine and Charity Hospital of Louisiana at New Orleans.

1 Neuberg, C., and Karczag, L. Ueber zuckerfreie Hefegärungen. IV. Carboxylase, ein neues Enzym der Hefe, *Biochem Ztschr* **36** 68-75, 1911.

2 Auhagen, E. Ueber Co-Carboxylase. Reinigungsversuche und Vorkommen in tierischen Organen, *Biochem Ztschr* **258** 330-339, 1933.

3 Lohmann, K., and Schuster, P. Ueber das Vorkommen der Adeninnucleotide in den Geweben rote Blutkörperchen. Das Molekulargewicht der Adenylpyrophosphorsäure, *Biochem Ztschr* **294** 183-187, 1937.

4 Ochoa, S., and Peters, R. A. Vitamin B₁ and Carboxylase in Animal Tissues, *Biochem J* **32** 1501-1515 (Sept) 1938.

5 Westenbrink, H. G. K., and Goudsmit, J. Investigations on Aneurin and Cocarboxylase Content of Animal Tissues, Estimated by Thiochrome Method, *Enzymologia* **5** 307-320, 1938.

6 Ochoa, S. Enzymic Synthesis of Cocarboxylase in Animal Tissues, *Biochem J* **33** 1262-1270 (Aug) 1939.

7 Tauber, H. Interaction of Vitamin B₁ in Enzymic Reactions, *J Biol Chem* **123** 499-506 (April) 1938.

8 Peters, R. A. Biochemical Lesion in Vitamin B₁ Deficiency, Application of Modern Biochemical Analysis in Its Diagnosis, *Lancet* **1** 1161-1165 (May 23) 1936.

9 Tonutti, E., and Wallraff, J. Wirkstoffe und Glykogenspeichungsvermögen der Leber, *Ztschr f mikr-anat Forsch* **44** 532-550, 1938.

10 Hermann, V. S. Ueber den Glykogenegehalt der Leber B₁ vitaminotischer Ratten, *Ztschr f physiol Chem* **262** 95-102 1939.

11 Longenecker, H. E., Gavin, G., and McHenry, E. W. Fatty Acids Synthesized by the Action of Thiamine, *J Biol Chem* **134** 693-699 (July) 1940.

dence of B₁ deficiency in patients proved to be suffering from hepatic disease and (2) the response of patients with hepatic disease to the administration of vitamin B₁

METHODS AND MATERIALS

A series of 32 patients suffering from various forms of hepatic disease was used. Most of these patients showed definite jaundice of varying degree. Routine studies of the blood, the urine and the stools were carried out. The renal function and the blood levels of urea nitrogen and nonprotein nitrogen were determined for each patient. Hepatic function was estimated by the cephalin flocculation test, the intravenous hippuric acid test and the bromsulphalein test. The pyruvic acid content of the blood was determined by the method

the blood of 6 "normal" patients were taken before and after the administration of equal doses of thiamine hydrochloride.

RESULTS

Of 32 persons suffering from various forms of hepatic disease, 27 showed definite evidence of vitamin B₁ deficiency as revealed by elevated levels of the blood levels of pyruvic acid. These levels varied from 1.5 to 4.25 mg. per hundred cubic centimeters (table 1). In the control series of patients the blood levels of pyruvic acid varied from 0.5 to 1.3 mg. per hundred cubic centimeters. Further analysis of the data was rendered difficult by the fact that in many of

TABLE 1—Blood Levels of Pyruvic Acid in Hepatic Disease

Patient	Age	Diagnosis	Fever	Nutrition	Icterus Index	Cephalin Flocculation Test	Hippuric Acid Test, Gm	Pyruvic Acid in Blood, Mg per 100 Cc
W ♀	52	Portal cirrhosis	0	Good	66.5	3+	0.27	3.0
W ♀	44	Cholangitis	+	Good	24.0			3.0
O ♂	24	Arsenical hepatitis	0	Good	140.0		0.86	1.85
W ♂	52	Obstructive jaundice due to retroperitoneal sarcoma	0	Good	126.0		0.6	2.0
W ♀	50	Cholangitis and hepatitis	+	Good	56.0	3+		2.25
O ♀	37	Obstruction of common bile duct	0	Good	16.0	0	0.77	0.85
O ♂	71	Carcinoma of head of pancreas	0	Poor	101.0	2+	0.4	2.3
W ♂	44	Amebic abscess of liver	+	Good	74.0	3+	0.36	4.25
W ♂	47	Portal cirrhosis	0	Good	208.0	3+	0.5	2.2
O ♀	52	Cholangitis and hepatitis	+	Good	126.0	3+	0.45	2.6
O ♀	42	Stone in common bile duct	0	Good	125.0		0.83	1.4
W ♂	48	Carcinoma of head of pancreas	0	Poor	62.5	0	0.14	2.5
W ♂	49	Well's disease	+	Good	113.0		0.42	3.0
W ♂	53	Obstructive jaundice due to retroperitoneal tumor	+	Good	50.0		0.7	0.43
W ♂	49	Hepatoma	0	Good	8.0	0	0.75	2.0
W ♂	53	Portal cirrhosis	0	Poor	12.5	0	0.3	2.2
W ♂	61	Portal cirrhosis	0	Good	43.0	2+	0.56	1.8
W ♂	63	Portal cirrhosis	+	Poor	62.0	4+	0.48	1.9
W ♂	46	Portal cirrhosis	0	Poor	10.0	0	0.6	2.4
W ♂	52	Portal cirrhosis	0	Good	20.0	0	0.6	1.8
W ♂	48	Hepatitis	+	Good	60.0	2+	0.5	2.6
W ♂	64	Neoplastic obstruction of common bile duct	+	Good	68.0	0	0.8	2.0
W ♂	35	Portal cirrhosis	+	Good	32.0	2+	0.28	1.5
W ♂	71	Hepatoma	0	Poor	9.0	0	0.85	1.5
W ♂	59	Portal cirrhosis	+	Poor	12.0	1+	0.53	1.5
W ♂	68	Catarrhal jaundice	+	Poor	40.0	2+	0.6	1.6
W ♂	32	Amebic abscess	+	Poor	45.0	2+	0.75	1.6
O ♂	68	Well's disease	+	Good	40.0	0	0.8	2.3
W ♂	71	Carcinoma of pancreas	0	Good	65.0	0	0.85	0.6
C ♀	38	Catarrhal jaundice	+	Good	62.0	0	0.8	1.5

of Lu¹² with the Klett-Summerson photoelectric colorimeter. Additional studies made were as to the Kline and the Kolmer reaction, the prothrombin content of the blood, the van den Bergh reaction, the total serum proteins, the serum albumin and the serum globulin. Roentgen studies of the gallbladder and of the gastrointestinal tract were carried out when indicated. A control group of 30 surgical patients suffering from minor ailments unassociated with fever was used (referred to later as "normal" patients). To determine the response of persons suffering from hepatic disease to the administration of vitamin B₁, the blood levels of pyruvic acid were determined before, and three hours after, the intramuscular injection of a standard amount of thiamine hydrochloride. Standard doses of 50 mg. or 100 mg. of thiamine hydrochloride were used. As controls, the levels of pyruvic acid in

hepatic disease was accompanied by fever, malnutrition or both. In an effort to evaluate the effects of diminished hepatic function, fever and malnutrition on the blood levels of pyruvic acid, the patients were arranged in four groups. In group 1 were 11 patients suffering from hepatic disease unaccompanied by fever or malnutrition. In group 2 were 10 patients suffering from hepatic disease with fever but without malnutrition. In group 3 were 4 patients suffering from hepatic disease accompanied by malnutrition but not by fever. In group 4 were 5 patients suffering from hepatic disease accompanied by fever and malnutrition. Each of these groups was further subdivided into (a) patients showing definite evidence of diminished hepatic function as revealed by tests for hepatic function and (b) patients in whom such tests revealed normal hepatic function.

12 Lu, G. D. Studies on Metabolism of Pyruvic Acid in Normal and Vitamin B Deficient States. Rapid Specific and Sensitive Method of Estimation of Blood Pyruvate, *Biochem J* 33: 249-254 (Feb) 1939.

tion The results are tabulated in table 2 In groups 1, 2 and 3 those patients with clinical evidences of diminished hepatic function showed

TABLE 2—*Evaluation of Effects of Diminution of Hepatic Function, Fever and Malnutrition on Blood Levels of Pyruvic Acid in Hepatic Disease*

Group 1 (11 Patients Without Fever or Malnutrition)		Group 2 (10 Patients With Fever but No Malnutrition)		Group 3 (4 Patients With Malnutrition but No Fever)	
(a) With Diminished Hepatic Function	(b) With Normal Hepatic Function	(a) With Diminished Hepatic Function	(b) With Normal Hepatic Function	(a) With Diminished Hepatic Function	(b) With Normal Hepatic Function
Pyruvic Acid in Blood, Mg per 100 Cc	Pyruvic Acid in Blood, Mg per 100 Cc	Pyruvic Acid in Blood, Mg per 100 Cc	Pyruvic Acid in Blood, Mg per 100 Cc	Pyruvic Acid in Blood, Mg per 100 Cc	Pyruvic Acid in Blood, Mg per 100 Cc
30	1.85	2.25	0.48	2.8	1.5
20	0.85	4.25	2.0	2.2	
22	1.4	2.6	2.3	2.4	
18	0.6	3.0	1.5		
18	0.8	2.5			
	2.0	1.5			
Av 2.16	Av 1.25	Av 2.68	Av 1.57	Av 2.46	Av 1.5

Note—Data on group 4 (patients with fever and malnutrition) are not included since all showed diminished hepatic function

table 3) Finally, if the patients are divided into two groups, those with decreased hepatic function and those with normal hepatic function, it is found that in the former group there are consistently higher blood levels of pyruvic acid and that the difference is statistically significant The second part of this investigation was concerned with a comparison of the response evidenced by reduction of the blood level of pyruvic acid to vitamin B₁ administered by intramuscular injection to "normal" patients and to those suffering from hepatic disease

The mean reduction in the pyruvic acid of the blood in "normal" patients three hours after the intramuscular injection of 50 mg of thiamine hydrochloride was 0.28 ± 0.074 mg per hundred cubic centimeters Injection of equal amounts in patients with hepatic disease but with normal hepatic function resulted in a greater reduction of the pyruvic acid of the blood, the mean being 0.6 ± 0.215 mg per hundred cubic centimeters This difference is statistically significant (horizontal column A table 4) However in patients

TABLE 3—*More Detailed Statistical Analysis of Groups in Table 2*

Group	Number of Patients	Pyruvic Acid in Blood, Mg per 100 Cc Mean	Difference Between Means *	t	P
Patients with diminished hepatic function without fever	5	2.16 ± 0.445			
Patients with diminished hepatic function with fever	6	2.65 ± 0.697	0.52	1.12	>0.2
Patients with normal hepatic function without fever	6	1.25 ± 0.536			
Patients with diminished hepatic function without fever	5	2.16 ± 0.445	0.91	2.716	<0.02
Patients with diminished hepatic function without fever or malnutrition	5	2.16 ± 0.445			
Patients with diminished hepatic function with malnutrition but no fever	3	2.46 ± 0.249	0.3	0.92	>0.3
Patients with normal hepatic function	11	1.38 ± 0.595			
Patients with diminished hepatic function	18	2.27 ± 0.537	0.89	4.009	<0.01

* Standard deviation = $\sqrt{\frac{\sum \Delta^2}{N}}$ P is derived from Fisher's table of t (Fisher R A Statistical Methods for search Workers London, Oliver & Boyd Ltd, 1938) The difference between the means of two groups is significant if is <0.05 Correction was made for small samples

consistently higher blood levels of pyruvic acid this suggests that diminished hepatic function may be one factor determining the elevation of the blood level of pyruvic acid in disease of the liver A more detailed statistical analysis of these groups is presented in table 3 In patients having definite evidences of decreased hepatic function fever does not appear to cause a statistically significant increase in the pyruvic acid of the blood (column A table 3) Decreased hepatic function is associated with increased content of pyruvic acid in the blood This increase is statistically significant (column B, table 3) The blood level of pyruvic acid in patients with decreased hepatic function and malnutrition is not significantly higher than that in the group without evidences of malnutrition (column C

with hepatic disease and decreased hepatic function the mean reduction is only 0.13 ± 0.099 mg per hundred cubic centimeters This response is statistically not significantly different from that which occurred in "normal" patients (horizontal column B, table 4) This is borne out by a comparison of the response to 50 mg of thiamine hydrochloride in patients with normal hepatic function with that in patients who had decreased hepatic function In the former group the mean reduction of the pyruvic acid in the blood is significantly greater (horizontal column C, table 4)

As might be expected, the administration of 100 mg of thiamine hydrochloride to "normal" patients leads to a greater mean reduction of pyruvic acid in the blood 0.52 ± 0.274 mg per

hundred cubic centimeters than does the administration of 50 mg of thiamine hydrochloride (horizontal column D, table 4) Moreover, this reduction is greater than that occurring in patients with decreased hepatic function (horizontal column E, table 4) The mean reduction of pyruvic acid in the blood after administration of 100 mg of thiamine hydrochloride is greater in patients whose hepatic function is normal, 0.7 ± 0.353 mg per hundred cubic centimeters, than in those whose hepatic function is decreased, 0.11 ± 0.07 mg per hundred cubic centimeters This difference is statistically significant (horizontal column E, table 4)

in dogs, and Rhoads and Miller¹⁶ found evidences of hepatic dysfunction in dogs suffering from experimentally induced "black tongue" Apart from the reduction in the glycogen and content of the liver in B₁ deficiency there appears to be no evidence to suggest that B₁ deficiency alone results in hepatic damage Our results on the other hand, indicate that the reverse situation may occur, namely, that hepatic damage may predispose to a state of B₁ deficiency It is of interest to inquire into the mechanism whereby hepatic damage predisposes to B₁ deficiency Clearly it is not due to a diminution of intake since this would affect all of the patients and

TABLE 4—Alteration of Blood Levels of Pyruvic Acid in Controls* and in Patients with Hepatic Disease After Parenteral Administration of Vitamin B₁

Group	Number of Patients	Amount of Thiamine Hydrochloride Injected Intra muscularly, Mg	Decrease in Pyruvic Acid in Blood, Mg per 100 Cc, Mean	Difference Between Means †	t	P
A Controls	5	50	0.28 ± 0.074			
Patients with hepatic disease and normal hepatic function	3	50	0.6 ± 0.215	0.32	2.64	<0.05
B Controls	5	50	0.28 ± 0.074			
Patients with hepatic disease and diminished hepatic function	3	50	0.13 ± 0.099	0.15	2.14	>0.05
C Controls	3	50	0.6 ± 0.215			
Patients with hepatic disease and diminished hepatic function	3	50	0.13 ± 0.099	0.47	3.906	<0.01
D Controls	2	100	0.52 ± 0.274			
Patients with hepatic disease and normal hepatic function	4	100	0.7 ± 0.353	0.18	0.614	>0.05
E Patients with hepatic disease and normal hepatic function	4	100	0.7 ± 0.353			
Patients with hepatic disease and diminished hepatic function	5	100	0.11 ± 0.07	0.59	2.78	<0.05

* Surgical patients with minor conditions unassociated with fever (normal patients)
† Correction was made for small samples

COMMENT

Since these results indicate a state of vitamin B₁ deficiency in patients suffering from various diseases of the liver, the question arises Can a deficiency of vitamin B₁ itself produce hepatic damage? Biskind and Biskind¹³ have found that a deficiency of the vitamin B complex in rats diminishes the ability of their livers to inactivate implanted estrone (theelin) Gyorgy and Goldblatt¹⁴ found that the livers of rats kept on a vitamin B-deficient diet undergo certain pathologic changes, specifically fatty degeneration, focal and massive necrosis, hyperemia and hemorrhage These changes were due not to deficiency of vitamin B₁ but to deficiency of some other part of the B complex possibly B₂ Other workers, also, have noted hepatic damage in animals fed a diet deficient in factors of the B complex, e g, Sebrell¹⁵ produced fatty infiltration of the liver

would not explain the difference in blood level of pyruvic acid between patients presenting evidences of diminished hepatic function and those presenting evidence of unaltered hepatic function There may be a defect in the absorption of vitamin B₁ from the intestine in patients with hepatic damage Machella and Elsom¹⁷ found that the urinary excretion of thiamine after it had been administered orally was lowered in patients with portal cirrhosis of the liver They attributed this to diminished intestinal absorption Undoubtedly, this may play a role, but it is probably not the only factor The data already presented in this paper indicate that the reduction of py

13 Biskind M S and Biskind G R Diminution in Ability of the Liver to Inactivate Estrone in Vitamin B Complex Deficiency Science 94 462 (No 14) 1941
14 György, P, and Goldblatt, H Hepatic Injury on a Nutritional Basis in Rats J Exper Med 70 185-192 (Oct) 1939

15 Sebrell, W H "Yellow Liver" of Dogs (Fatty Infiltration) Associated with Deficient Diets, Bulletin 162, National Institute of Health, United States Treasury Department, Public Health Service, 1933 12 23-35
16 Rhoads C P and Miller, D K Hepatic Dysfunction in Dogs Fed Diets Causative of Black Tongue J Exper Med 67 463-467 (March) 1938
17 Machella T E, and Elsom, K O Urinary Excretion of Ingested Thiamine in Patients with Chronic Hepatic Disease, Am J M Sc 202 512-516 (Oct) 1941

ruvic acid in the blood after administration of thiamine is significantly less in patients with reduced hepatic function than in those whose hepatic function is normal. This would suggest that the liver itself may be at fault. Since phosphorylation of vitamin B₁ takes place in the liver, as has been shown by Ochoa and Peters⁴ and by Westenbrink and Goudsmit,⁵ it is suggested that phosphorylation of vitamin B₁ is diminished in certain forms of hepatic disease. Thus, less thiamine would be available physiologically for utilization by the tissues, leading to an elevation of the blood level of pyruvic acid and to other evidences of vitamin B₁ deficiency.

SUMMARY AND CONCLUSIONS

Thirty-two patients suffering from various forms of hepatic disease were studied as was also a control group of 30 surgical patients who had minor conditions unassociated with fever ("normal" patients). Vitamin B₁ deficiency as revealed

by elevated blood levels of pyruvic acid was present in 28 of the 32 patients. Fever, malnutrition and diminished hepatic function, as determined by various clinical tests, frequently accompany hepatic disease. The reduction of hepatic function appears to be the most significant etiologic factor underlying the elevation of the blood level of pyruvic acid in such patients. Following the intramuscular injection of a standard dose of thiamine hydrochloride, the pyruvic acid in the blood diminishes both in normal persons and in patients with hepatic disease. The decrease in the pyruvic acid of the blood after administration of vitamin B₁ is significantly less when hepatic function is diminished. It is suggested that hepatic disease when associated with diminished hepatic function is a primary factor in inducing a state of vitamin B₁ deficiency, because of diminished hepatic capacity to phosphorylate vitamin B₁ and thus render it available for utilization by the tissues.

VITAMIN B₁ NUTRITION IN SURGICAL PATIENTS AS DETERMINED BY THE BLOOD LEVEL OF PYRUVIC ACID

II THYROID DISEASE

HARRY A DAVIS, MD, AND FRANZ K BAUER, MD

NEW ORLEANS

A considerable diversity of opinion exists regarding the relationship between vitamin B₁ and the function of the thyroid gland. It was not until Cowgill¹ demonstrated that the vitamin B₁ requirement of man is increased by elevation of the metabolic rate that the role played by this vitamin in thyrotoxicosis became the subject of much study. The purpose of the present investigation was to determine the nutritional status with respect to vitamin B₁ of persons suffering from toxic and nontoxic thyroid disease. The consistent rise in the pyruvic acid of the blood in vitamin B₁ deficiency provides a quantitative method of estimating the extent of this deficiency

are similar to those found by Bueding and Wortis.³ Seven patients with nontoxic goiter exhibited blood levels of pyruvic acid varying from 0.45 mg to 1.3 mg per hundred cubic centimeters. In 16 cases of thyrotoxicosis associated with nontoxic or diffuse goiter the pyruvic acid content of the blood varied from 1.45 mg to 3.5 mg per hundred cubic centimeters (table 1). While all these values were definitely raised, there did not appear to be an exact correlation between the increase of the metabolic rate or of the pulse rate and that of the pyruvic acid in the blood (table 1). Likewise, there did not appear to be an

METHODS AND MATERIALS

Immediately on admission of the patient to the hospital the pyruvic acid content of the blood was determined by the method of Lu² with a Klett-Summerson photoelectric colorimeter. Hepatic function was estimated by the intravenous hippuric acid test or by the galactose tolerance test. Metabolic and blood chemical studies were carried out routinely on all of the patients with thyroid disease. A series of 23 patients was used, of whom 16 were suffering from toxic and 7 from nontoxic thyroid disease. A control series was used consisting of 30 surgical patients suffering from various minor ailments unassociated with fever. All of the patients having thyroid disease were subjected to operation, so that it was possible to verify histologically the lesion in each gland. All of the thyrotoxic patients were placed on a high carbohydrate, high protein and low fat diet (2,000 calories daily).

RESULTS

The control series was composed of 14 white and 16 Negro patients suffering from minor nontoxic conditions and varying in age from 18 to 60 years. In this group the pyruvic acid content of the blood ranged from 0.5 mg to 1.3 mg per hundred cubic centimeters. These values are somewhat higher than those obtained by Lu² but

TABLE 1—Blood Levels of Pyruvic Acid in Thyrotoxicosis

Patient	Color	Age	Sex	Type of Goiter	Pulse Rate	Basal Metabolic Rate	Pyruvic Acid in Blood, Mg per 100 cc.
D M	Negro	18	F	Diffuse toxic	120	+72	1.8
N H	Negro	27	F	Diffuse toxic	140	+76	1.6
K G	Negro	32	F	Diffuse toxic	116	+25	1.6
W S	Negro	21	M	Diffuse toxic	100	+19	1.5
L R	Negro	54	F	Diffuse toxic	140	+60	1.6
M T	White	33	F	Diffuse toxic	130	+59	3.5
R B	White	27	M	Nodular toxic	120	+38	1.5
B F	White	27	M	Diffuse toxic	120	+14	1.5
M G	White	55	M	Nodular toxic	120	+51	2.5
O D	White	39	F	Diffuse toxic	124	+41	1.4
O B	White	38	F	Nodular toxic	100	+15	1.6
E G	White	19	F	Diffuse toxic	120	+38	1.8
M T	White	40	F	Diffuse toxic	140	+23	1.9
M G	Negro	52	F	Diffuse toxic	124	+76	1.8
I H	Negro	26	F	Diffuse toxic	130	+30	2.1
C F	Negro	56	F	Diffuse toxic	140	+50	2.4

correlation between the pyruvic acid content of the blood and the type of toxic goiter present, whether diffuse or nodular. These data appear to suggest that vitamin B₁ malnutrition exists in patients suffering from thyrotoxicosis as revealed by elevation of the blood levels of pyruvic acid.

It was now necessary to investigate the effect of treatment on the blood levels of pyruvic acid. For this purpose two groups of patients were used. To one group strong solution of iodine, U S P and vitamin B₁ (thiamine hydrochloride)

From the Department of Surgery of the Louisiana State University School of Medicine and Charity Hospital of Louisiana at New Orleans.

1 Cowgill, G R. Vitamin B Requirement of Man. New Haven Conn: Yale University Press, 1934.

2 Lu, G D. Studies on Metabolism of Pyruvic Acid in Normal and Vitamin B₁-Deficient States. Rapid, Specific and Sensitive Method for Estimation of Blood Pyruvate, Biochem J **33**: 249-254 (Feb) 1939.

3 Bueding, E, and Wortis, H. The Stabilization and Determination of Pyruvic Acid in the Blood. J Biol Chem **133**: 585-591 (April) 1940.

ride) were given in addition to the diet already described. The second group received the same diet and strong solution of iodine U S P only. The results obtained in these two groups are illustrated in table 2. Before treatment the mean value for pyruvic acid in the blood of 11 patients was 1.84 ± 0.563 mg per hundred cubic centimeters. After treatment with strong solution of iodine (0.9 cc three times a day) and thiamine hydrochloride (10 mg three times a day) the value for pyruvic acid in the blood dropped to 1.12 ± 0.302 mg per hundred cubic centimeters. This difference in values for pyruvic acid is statistically significant (table 2) and is not due to errors of sampling. The second group of patients before treatment had a mean value for pyruvic acid in the blood of 2.0 ± 0.228 mg per hundred cubic centimeters. After treatment with

tions of the pyruvic acid in the blood of thyrotoxic patients were affected by race. No significant difference could be found between white and Negro patients (table 2).

COMMENT

The results which have been presented strongly suggest that a disturbance of the carbohydrate metabolism leading to an accumulation of pyruvic acid in the blood occurs in thyrotoxicosis. A considerable amount of speculation has arisen regarding the exact role played by vitamin B₁ deficiency in thyrotoxicosis. Certain workers, such as Sure and Buchanan⁴ and Peters and Rossiter,⁵ have expressed the belief that vitamin B₁ physiologically counteracts the effects of thyroxin. On the other hand, Elmer and his co-workers,⁶ Gentzen and Mohr⁷ and Parade⁸ can-

TABLE 2—Response of Blood Levels of Pyruvic Acid in Thyrotoxic Patients to Treatment

Time of Determination in Relation to Treatment	Number of Patients	Pyruvic Acid in Blood Mg per 100 Cc, Mean	Difference Between Means *	t	P
White patients (before treatment)	8	1.975 ± 0.623			
Negro patients (before treatment)	8	1.812 ± 0.279	0.163	0.631	>0.05
before treatment	11	1.84 ± 0.563			
after treatment (thiamine hydrochloride and strong solution of iodine U S P)	11	1.12 ± 0.302	0.72	3.52	<0.01
before treatment	5	2.0 ± 0.228			
after treatment (strong solution of iodine U S P)	5	1.64 ± 0.1	0.36	2.9	<0.02
before thyroidectomy	10	1.16 ± 0.31			
days after thyroidectomy	10	1.35 ± 0.23	0.19	2.73	<0.02
Decrease in Blood Pyruvic Acid, Mg per 100 Cc, Mean					
after treatment (thiamine hydrochloride and strong solution of iodine U S P)	11	0.66 ± 0.33			
after treatment (strong solution of iodine U S P)	5	0.36 ± 0.17	0.3	1.754	>0.05

* Correction has been made for small samples. P is derived by use of Fisher's table of t (Fisher, R. A. Statistical Methods for Research Workers, London, Oliver & Boyd Ltd 1938). The difference between the means of two groups is significant if P is <0.05.

strong solution of iodine U S P alone the value for pyruvic acid fell to 1.64 ± 0.1 mg per hundred cubic centimeters. This decrease is statistically significant and not due to errors of sampling (table 2). In both groups there was concomitant reduction of the basal metabolic rate and pulse rate, but this reduction was not quantitatively related to the fall in the blood pyruvic acid. A comparison of the blood levels of pyruvic acid after treatment with strong solution of iodine U S P only and after treatment with this solution plus vitamin B₁ shows that there is no significant difference (table 2). Eight days after subtotal thyroidectomy had been performed the blood levels of pyruvic acid were again determined. At this interval after thyroidectomy some patients exhibited a fall in pyruvic acid. However, many showed an elevation which was statistically significant (table 2). Finally, it was of interest to determine whether or not the eleva-

tion of pyruvic acid in the blood of thyrotoxic patients was affected by race. No significant difference could be found between white and Negro patients (table 2). It is well known that a diminu-

4 Sure, B., and Buchanan, K. S. Antithyrogenic Action of Crystalline Vitamin B₁, J. Nutrition **13** 513-519 (May) 1937.

5 Peters, R. A., and Rossiter, R. J. Thyroid and Vitamin B₁, Biochem J **33** 1140-1150 (July) 1939.

6 Elmer, A. W., Giedosz, B., and Scheps, M. L'action de la vitamine B₁ dans l'hyperthyroïose expérimentale, Compt rend Soc de biol **126** 1037-1038, 1937.

7 Gentzen, G., and Mohr, T. Experimenteller Beitrag zur Frage der Beziehungen zwischen Vitamin B₁ und Schilddrüse, Klin Wchnschr **17** 1243-1245 (Sept 3) 1938.

8 Parade, G. W. Der Einfluss der Schilddrüsenverabreichung bei Hunger und Vitamin B₁-Mangel, Ztschr f Vitaminforsch **7** 40-45 (Jan) 1938.

9 Drill, V. A. The Effect of Experimental Hyperthyroidism on the Vitamin B₁ Content of Some Rat Tissues, Am J Physiol **122** 486-490 (May) 1938.

tion of hepatic function frequently is present in thyrotoxicosis. The question arises: Is this diminution related to the disturbance of carbohydrate metabolism either as a cause or as an effect? Drill and his co-workers¹⁰ have presented evidence indicating that the reduction of hepatic function in dogs with hyperthyroidism can be delayed by supplemental administration of vitamin B₁ and yeast. The relationship of vitamin B₁ to hepatic function and hepatic disease has been discussed more fully in the first paper of this series. Certain other factors are present in thyrotoxicosis which serve to intensify the nutritional deficit with respect to vitamin B₁. Hardt and Still¹¹ have shown that 5 to 15 per cent of ingested vitamin B₁ is lost in the sweat. Since patients with thyrotoxicosis perspire freely, a considerable amount of vitamin B₁ may be lost in this way. This loss is not compensated for by diminution in the output of vitamin B₁ in the urine. Another factor accentuating the lack of vitamin B₁ is the high carbohydrate diet which is customarily administered to such patients prior to operation. Environmental temperatures affect vitamin B₁ requirements. Mills¹² has pointed out that the higher the environmental temperature the greater the need for vitamin B₁. He has estimated that the optimal requirement for vitamin B₁ per gram of food is twice as high at 91 F as it is at 65 F. The intolerance of the severely thyrotoxic patient for heat and the well known increased tendency toward thyroid crisis exhibited during the summer by thyrotoxic patients living in tropical and subtropical climates may be due in part to a heat-accentuated deficiency of vitamin B₁. In the data which we have presented the group of patients receiving vitamin B₁ in addition to strong solution of iodine U S P did not show a greater diminution of pulse rate or of metabolic rate than did the group

of patients who received only strong solution of iodine. This is in agreement with the work of Frazier and his co-workers¹³.

The elevation of the blood level of pyruvic acid exhibited by some patients during the first few days after subtotal thyroidectomy merits further discussion. This suggests that subtotal thyroidectomy itself may precipitate a minor degree of vitamin B₁ deficiency. Pollack and his co-workers¹⁴ have reported the occurrence of ariboflavinosis after surgical operation. Our results would seem to indicate the advisability of administering increased amounts of vitamin B₁ and possibly of other members of the B complex to thyrotoxic patients after surgical operation.

SUMMARY AND CONCLUSION

The nutritional status with respect to vitamin B₁ of 23 patients suffering from thyroid disease was studied. A control series of 30 relatively normal patients was used. The blood level of pyruvic acid in the control patients ranged from 0.5 mg to 1.3 mg per hundred cubic centimeters. Seven patients suffering from nontoxic goiter showed blood levels of pyruvic acid varying from 0.45 mg to 1.3 mg per hundred cubic centimeters, which are normal values. Sixteen patients suffering from toxic diffuse goiter or toxic nodular goiter revealed blood levels of pyruvic acid which varied from 1.45 mg to 3.5 mg per hundred cubic centimeters.

No significant differences were noted between the blood levels of pyruvic acid in Negro and in white patients. The administration of strong solution of iodine U S P alone results in a definite reduction of the pyruvic acid in the blood. Similarly, the administration of this solution and vitamin B₁ results in a decrease in the pyruvic acid of the blood, this decrease being statistically significant. Subtotal thyroidectomy may induce temporarily an increased need for vitamin B₁ as revealed by postoperative elevation of the blood level of pyruvic acid.

10 Drill, V. A., and Hays, H. W. Studies on the Relation of the Liver Function, Pulse Rate and Temperature of Hyperthyroid Dogs to Vitamin B₁ and Yeast, *Am J Physiol* **136** 762-771 (July) 1942. Drill, V. A., Schaffer, C. B., and Overman, R. Liver Function, Pulse Rate and Temperature of Hyperthyroid Dogs, *ibid* **138** 370-377 (Jan) 1943.

11 Hardt, L. L., and Still, E. U. Thiamin in Sweat, *Proc Soc Exper Biol & Med* **48** 704-707 (Dec.) 1941.

12 Mills, C. A. Environmental Temperatures and Thiamine Requirements, *Am J Physiol* **133** 525-531 (July) 1941.

13 Frazier, W. D., Brown, R. B., and Vars, H. M. The Influence of the B Complex and Certain of Its Components on Experimental and Clinical Hyperthyroidism, *Tr Am A Study Goiter*, 1939, pp 247-255.

14 Pollack, H., Ellenberg, M., and Dolger, H. Postoperative Precipitation of Vitamin B Complex Deficiencies. *J Mt Sinai Hosp* **8** 925-932 (Jan-Feb) 1942.

VITAMIN B₁ NUTRITION IN SURGICAL PATIENTS AS DETERMINED BY THE BLOOD LEVEL OF PYRUVIC ACID

III RENAL DISEASE, NEOPLASTIC DISEASE AND INFECTION

HARRY A DAVIS, MD, AND FRANZ K BAUER, MD

NEW ORLEANS

It has been shown in previous papers that persons suffering from hepatic disease or from toxic thyroid disease present evidence of vitamin B₁ malnutrition as revealed by the blood levels of pyruvic acid. The present paper is concerned with a study of persons suffering from renal disease, neoplastic disease and infection.

RENAL DISEASE

The kidney plays a significant role in the metabolism of vitamin B₁. Greater amounts of this vitamin are present in the liver, heart, brain, muscles and kidneys than in other tissues. The kidneys excrete a considerable quantity of the vitamin daily. This excretion continues, but to a lesser extent, even in the presence of vitamin B₁ deficiency. Finally, renal tissue is one of the tissues which can convert vitamin B₁ into cocarboxylase (Westenbrink and Goudsmit¹). In view of these facts the question arises: In the presence of renal disease is there diminished phosphorylation and excretion of vitamin B₁ by the kidneys? Eleven patients with various forms of renal disease were studied. Blood levels of pyruvic acid were determined by the method of Lu². The usual tests of renal function were carried out. The results are given in table 1. It will be noted that in this series of 11 patients only 2 presented elevated blood levels of pyruvic acid. One of them was anuric. Since this patient was receiving dextrose infusions, the increase of pyruvic acid in his blood cannot be considered significant. Despite marked azoemia and other evidences of severe failure of renal function in many of these patients the blood levels of pyruvic acid did not indicate the presence of vitamin B₁ deficiency. This may be

significant in view of the fact that 5 of the 11 patients showed definite signs of malnutrition. The possibility must be considered that there is diminished excretion of thiamine hydrochloride when a diminution of renal function is present.

NEOPLASTIC DISEASE

Relatively few studies have been made of the relationship of vitamin B₁ to malignant neoplastic disease. Bischoff and Long³ reported that vitamin B₁ did not affect the rate of tumor growth in mice although it did affect the nutritional status and somatic growth of these animals. Masayama and Yokoyama⁴ found that rats with experimentally produced carcinoma of the liver had greater amounts of vitamin B₁ in the liver, spleen, heart and muscles than did normal rats. They also noted that vitamin B₁ was present in the cancer itself. These findings are in direct contrast with those of Schneider and Burger⁵ who, using the thiochrome method of Jansen, found a reduction of the vitamin B₁ content of the urine and the blood serum of patients with cancer. The question arises: Is a deficiency of vitamin B₁ present in patients with malignant neoplastic disease? In order to answer this question, a series of 19 patients with various forms of cancer was studied. The data are presented in table 2. The patients were divided into three groups: group 1, patients with cancer who had neither fever nor malnutrition; group 2, patients having either fever or malnutrition; group 3, patients presenting fever and malnutrition. In group 1 were 9 patients. Their pyruvic acid levels varied from 0.5 mg to 2.25 mg per hundred cubic centimeters of blood, the mean was 1.31 ± 0.598 mg. This figure represents

From the Department of Surgery of the Louisiana State University School of Medicine and Charity Hospital of Louisiana at New Orleans.

1 Westenbrink, H. G. K., and Goudsmit, J. Investigations on Aneurin and Cocarboxylase Content of Animal Tissues, Estimated by Thiochrome Method, *Enzymologia* 5: 307-320, 1938.

2 Lu, G. D. Studies on Metabolism of Pyruvic Acid in Normal and Vitamin B₁-Deficient States: Rapid Specific and Sensitive Method of Estimation of Blood Pyruvate, *Biochem J* 33: 249-254 (Feb) 1939.

3 Bischoff, F., and Long, M. L. The Relation of the Vitamin B Complex to Tumor Growth, *Am J Cancer* 37: 54-58 (Sept) 1939.

4 Masayama, T., and Yokoyama, T. Ueber den Gehalt an Aneurin sowie Co-Carboxylase im Krebsgewebe und in verschiedenen Organen der Leberkrebsratte, *Gann* 34: 178-179 (June) 1940.

5 Schneider, E., and Burger, A. Der Vitamin-B₁-Spiegel im Blut und Urin und seine Veränderungen bei den Hyperthyreosen und bei der Krebskachexie, *Klin Wchnschr* 17: 905-907 (June 25) 1938.

the upper limit of the normal level. The figures indicate that vitamin B₁ deficiency is not a constant finding in persons suffering from malignant neoplastic disease unaccompanied by fever or malnutrition. In group 2 were 8 patients with cancer and definite evidences of malnutrition but without fever. Their blood levels of pyruvic acid varied from 1.5 mg to 4.25 mg per hundred cubic centimeters, the mean level being 1.88 ± 0.897 mg. These data indicate

Of 19 persons suffering from malignant neoplastic disease, 14 presented vitamin B₁ malnutrition as shown by elevated blood levels of pyruvic acid. This appears to be due in part at least to associated malnutrition or fever. Vitamin B₁ malnutrition in malignant neoplastic disease may result also from deficient ingestion, digestion, absorption or utilization of vitamin B₁. The data (table 2) do exhibit a trend pointing to a relationship between the duration of the

TABLE 1—Blood Levels of Pyruvic Acid in Renal Disease

Patient	Age	Diagnosis	Fever	Nutrition	Blood Urea Nitrogen, Mg per 100 Cc	Blood CO ₂ Combining Power, Vol per Cent	Phenol sulphathiazine Test, per Cent	Pyruvic Acid in Blood, Mg per 100 Cc
White ♂	42	Malignant hypertension with renal insufficiency	0	Poor	65.0	30	55	0.95
White ♂	12	Chronic glomerulonephritis	0	Poor	13.4	50	75	0.6
White ♂	20	Mercury bichloride poisoning	0	Good	60.0	22	Anuria	1.0
White ♂	56	Chronic glomerulonephritis	0	Good	22.8	45		0.6
Negro ♂	51	Urinary retention due to prostatic carcinoma	0	Good	86	26	30	2.25
White ♂	15	Acute glomerulonephritis	+	Good	21	30	40	0.5
Negro ♀	16	Acute glomerulonephritis	0	Poor	31	35	30	0.8
Negro ♀	21	Acute glomerulonephritis	0	Poor	26	36	40	0.6
Negro ♀	27	Chronic glomerulonephritis	0	Good	42	35	25	1.0
Negro ♀	65	Urinary retention due to prostatic hypertrophy	0	Good	30	44	45	1.0
Negro ♂	65	Urinary retention due to carcinoma of bladder	+	Poor (recently log dextrose infusions)	61	22	Anuria	2.8

TABLE 2—Blood Levels of Pyruvic Acid in Malignant Neoplastic Disease

Patient	Age	Diagnosis	Duration of Symptoms	Fever	Nutrition	Pyruvic Acid in Blood, Mg per 100 Cc
Negro ♀	45	Carcinoma of uterus	2 mo	0	Poor	1.5
Negro ♀	55	Carcinoma of uterus	6 mo	0	Good	1.2
White ♀	67	Carcinoma of breast, grade III	6 mo	0	Poor	1.5*
Negro ♀	45	Carcinoma of breast grade IV	8 mo	+	Poor	2.5
Negro ♀	63	Carcinoma of ovary with metastases	2 yr	0	Poor	4.25
White ♂	49	Hepatoma	6 mo	0	Good	2.0*
Negro ♂	66	Carcinoma of rectum	1 yr	0	Good	1.0
Negro ♂	67	Carcinoma of bladder	2 yr	0	Poor	1.7*
White ♂	69	Sarcoma of thigh	3 mo	0	Good	0.5
White ♀	32	Fibrosarcoma of thigh	1 yr	0	Good	1.0
White ♂	45	Carcinoma of head of pancreas	15 mo	+	Poor	2.8
Negro ♂	81	Carcinoma of prostate gland	3 yr	0	Good	2.25
Negro ♂	63	Carcinoma of rectum	1 yr	0	Poor	1.5
White ♂	55	Retroperitoneal sarcoma	1 yr	0	Good	0.48
White ♀	12	Retroperitoneal sarcoma	6 mo	0	Good	1.0
Negro ♂	52	Carcinoma of stomach	3 mo	0	Poor	1.6*
White ♂	56	Carcinoma of stomach	1 yr	0	Poor	1.5*
Negro ♀	53	Carcinoma of stomach	6 mo	0	Poor	1.5*
Negro ♀	33	Carcinoma of stomach	3 mo	0	Good	1.8

* These patients received vitamin B₁ supplements daily.

that persons suffering from cancer accompanied by malnutrition but not by fever have vitamin B₁ malnutrition, as revealed by consistently elevated blood levels of pyruvic acid. The significance of these figures is increased when it is noted that 5 of the 8 patients were receiving supplemental thiamine hydrochloride in doses of 5 to 10 mg three times a day. In group 3 there were only 2 patients. In both of these the blood levels of pyruvic acid were elevated, the average being 2.65 ± 0.15 mg per hundred cubic centimeters. As might be expected, these patients showed more evidences of vitamin B₁ malnutrition than did the patients of either group 1 or group 2.

disease and the increase of pyruvic acid in the blood. This relationship does not appear in all instances.

INFECTION

There have been few studies of the nutritional status with respect to vitamin B₁ of persons suffering from infection associated with fever. Tangari,⁶ using Schopfer's method, noted a decrease in the vitamin B₁ content of the blood in acute experimental peritonitis. For these

6 Tangari C. Comportamento delle vitamine del sangue nelle peritoniti acute sperimentali, *Med. sper. Arch. ital.* 6:169-178 (March) 1940.

reasons a series of 38 patients with various types of infection was investigated to determine the presence or the absence of vitamin B₁ deficiency

TABLE 3—*Influence of Surgical Infections on Blood Levels of Pyruvic Acid*

Patient Sex Age	Diagnosis	Duration of Fever	White Blood Cells per Cu Mm	Pyruvic Acid in Blood, Mg per 100 Ce
♂ 22	Postoperative infection	1 day	8,600	1.6
♂ 67	Extravasation of urine	1 day	12,000	1.8
♀ 45	Acute appendicitis	1 day	11,000	1.2
♀ 45	Perineal abscess	1 day	18,600	0.6
♀ 26	Acute pelvic inflammatory disease	1 day	10,000	1.0
♀ 17	Acute pelvic inflammatory disease	1 day	15,100	1.7
♀ 20	Acute pelvic inflammatory disease	1 day	10,000	1.2
♀ 17	Acute appendicitis	1 day	11,000	1.0
♀ 28	Acute pelvic inflammatory disease	2 days	8,100	1.0
♀ 21	Acute pelvic inflammatory disease	2 days	8,500	1.3
♀ 15	Acute appendicitis	2 days	16,000	1.3
♂ 63	Extravasation of urine	2 days	10,000	1.5
♂ 21	Acute appendicitis	2 days	10,500	0.8
♂ 18	Acute appendicitis	2 days	9,600	1.6
♂ 17	Acute appendicitis	2 days	12,000	1.2
♂ 27	Acute appendicitis	2 days	11,000	1.0
♂ 43	Urethritis	2 days	6,500	0.8
♀ 22	Postoperative infection	2 days	15,000	1.5
♀ 51	Perirectal abscess	3 days	10,000	1.2
♀ 22	Acute pelvic inflammatory disease	3 days	7,800	0.9
♀ 18	Acute appendicitis	3 days	8,600	1.5
♀ 20	Incomplete septal abortion	3 days	18,000	1.5
♀ 20	Acute pelvic inflammatory disease	3 days	10,000	1.6
♀ 24	Acute pelvic inflammatory disease	3 days	13,000	1.3
♀ 37	Postoperative infection	4 days	19,000	1.9
♀ 16		4 days	7,200	0.8
♀ 64		5 days	6,800	1.7
♀ 31		5 days	9,000	1.45
♀ 50	Ductal gangrene	5 days	12,000	1.5
♀ 28	Acute thrombophlebitis	5 days	14,000	0.5
♀ 45		5 days	10,000	1.0
♀ 13		5 days	9,000	2.2
♀ 60		6 days	9,000	2.1
♀ 14	Jaundice	7 days	7,000	1.2
♀ 32	Closed space infection of finger	7 days	5,800	1.2
♀ 52	Abscess of lung	18 days	12,000	1.6*
♀ 32	Abscess of lung	36 days	8,400	1.7*
♀ 20	Acute osteomyelitis of skull	18 days	10,600	1.5*

* These patients were receiving supplemental amounts of vitamin B₁

In table 3 the patients have been grouped according to the duration of fever. Of 35 patients having fever lasting from one to seven days, 15

expected to occur among the normal hospital population. None of these patients received supplemental vitamin B₁. Three patients having various types of infection with fever lasting more than seven days all showed elevated blood levels of pyruvic acid despite the fact that all were receiving supplemental vitamin B₁ (table 3).

No statistically significant differences in blood levels of pyruvic acid appear between white and Negro patients (table 4). If our observations are confined to patients having infection with fever of a duration not exceeding seven days, it appears from the data presented that the duration of fever is not a significant factor in producing an elevation of the blood level of pyruvic acid. Thus, 26 patients with fever lasting from one to four days showed a mean value for pyruvic acid of 1.26 ± 0.337 mg per hundred cubic centimeters, whereas 9 patients with fever of five to seven days' duration had a mean value for pyruvic acid of 1.42 ± 0.502 mg per hundred cubic centimeters. There is no statistically significant difference between these two values (table 4). As has already been stated, 15 of 35 patients had elevated blood levels of pyruvic acid. Comparison of these levels with those of the remaining 20 patients reveals a significant difference since P is < 0.01 (table 4). The factors leading to abnormally high levels of pyruvic acid in the presence of infection with fever of short duration are not clear. There does not appear to be any correlation between such levels and the degree of constitutional reaction to infection as exemplified by the leukocyte count (table 3). The extent of tissue involved in the inflammatory process may be a factor influencing the level of pyruvic acid. Elevated levels appear to occur more frequently in association with postoperative febrile disturbances and infections (table 3). Certain of these patients might have been in a state of vitamin B₁ malnutrition before the onset of infection. Under such circum-

TABLE 4—*Effect of Surgical Infections on Blood Levels of Pyruvic Acid*

Groups	Number of Patients	Pyruvic Acid in Blood Mg per 100 Ce, Mean	Difference Between Means	t	P*
White patients with fever lasting 1 to 7 days	12	1.27 ± 0.357			
Negro patients with fever lasting 1 to 7 days	23	1.31 ± 0.357	0.04	0.377	> 0.7
Patients with fever lasting 1 to 7 days—group a	20	1.01 ± 0.23			
Patients with fever lasting 1 to 7 days—group b	15	1.67 ± 0.222	0.66	5.0	< 0.01
Patients with fever lasting 1 to 4 days	26	1.26 ± 0.337			
Patients with fever lasting 5 to 7 days	9	1.42 ± 0.502	0.16	0.68	> 0.3

* P is derived from Fisher's table of t (Fisher R. A. Statistical Methods for Research Workers London Oliver & Boyd Ltd 1935). In comparing two groups P is significant if it is < 0.05 .

stances the pyruvic acid levels might become elevated more readily. This could explain the occurrence of abnormally high blood levels of

pyruvic acid. This could explain the occurrence of abnormally high blood levels of

pyruvic acid in 3 of 8 patients after fever of only one day's duration (table 3)

CONCLUSIONS AND SUMMARY

The blood levels of pyruvic acid have been studied in three groups of patients. In a series of 11 persons suffering from various forms of renal disease the pyruvic acid in the blood was not increased despite the fact that azotemia was present in many of these patients. One patient with anuria and uremia showed a normal blood level of pyruvic acid. In only 2 patients was the blood level of pyruvic acid elevated. One of these patients had fever, to which the elevation of blood pyruvic acid could be attributed. The second patient was receiving dextrose infusions, and this could explain the elevation of the pyruvic acid in his blood. These facts suggest that renal disease even when associated with severe failure of renal function is not accom-

panied by an increase of the pyruvic acid in the blood. The possibility exists that patients with severe renal disease are protected to some extent against the onset of vitamin B₁ deficiency by diminution of the excretion of the vitamins in the urine. A second group of patients was studied. This consisted of 19 persons suffering from malignant neoplastic disease. It was found that in such patients vitamin B₁ malnutrition as shown by an elevation of the blood level of pyruvic acid might occur even in the absence of fever and obvious malnutrition. The levels were more likely to be elevated, however, when fever and malnutrition also were present.

The third group studied consisted of 38 persons suffering from various types of infection associated with elevation of the body temperature. It was found that 18 of these patients had vitamin B₁ malnutrition as revealed by an increase in the blood levels of pyruvic acid.

TWO STAGE OPERATION FOR CARCINOMA OF TRANSVERSE COLON PRODUCING DUODENOCOLIC FISTULA

REPORT OF TWO CASES

ROBERT R LINTON, MD

BOSTON

Numerous articles demonstrating the feasibility of the surgical removal of the duodenum and the head of the pancreas for carcinoma involving one or both of these organs have appeared in the surgical literature since Whipple¹ reported the successful extirpation of the head of the pancreas in 1938. Colectomy of the right side in either one or two stages, for malignant lesions involving the cecum, ascending colon or hepatic flexure, is a well recognized surgical procedure which carries a relatively low mortality rate.

The cases reported in this communication are of interest because they present instances of primary carcinoma of the proximal portion of the transverse colon which had eroded the second portion of the duodenum, producing a large fistulous opening between the two lumens of the bowel. Removal required colectomy of the right side and in addition necessitated the carrying out of the Whipple type of operation for carcinoma of the pancreas. This was successfully performed in both cases. The operative procedure was done in two stages because the patients were in a serious state of malnutrition from the malignant condition and their inability to assimilate food due to the duodenocolic fistulas. In addition the danger of severe post-operative infection would have been much greater in a one stage operation, since all the lumens of the bowel including the stomach and duodenum contained highly infective fecal material because of the communication between the duodenum and the colon. The first stage of the operation consisted in by-passing the fistula by transecting the stomach and terminal ileum and performing a gastrojejunostomy and an ileotransverse colostomy. The second stage consisted of the removal of the primal growth and the involved organs after the patient's nutritional state had been improved.

From the Surgical Service of the Massachusetts General Hospital

¹ Whipple, A O. Surgical Treatment of Carcinoma of the Ampullary Region and Head of the Pancreas, *Am J Surg* 40:260 (April) 1938.

REPORT OF CASES

CASE 1—History—P B, a 59 year old Italian man, a worker in a pottery shop, was admitted to the Massachusetts General Hospital Nov 13, 1941. The chief complaint was vomiting and watery diarrhea of five months' duration, worse in the last week. He was well until six months before admission except for occasional attacks of indigestion. At this time mild epigastric distress developed, with gas and belching occurring a few hours after eating. He vomited several times a week. The vomitus consisted largely of bile, rarely of food. Prior to one year before admission his bowels moved two to four times weekly. Approximately one year before he began having movements daily and three months before admission diarrhea commenced, with five to fifteen movements each day. During the past few weeks on numerous occasions he had noted the passage of undigested food in his stools, eaten only fifteen minutes before. One week before his admission daily nausea and vomiting developed. He had lost 20 pounds (9.1 Kg) in weight, from 185 to 165 pounds (83.9 to 74.8 Kg), during the past three months. He had dyspnea on exertion of one year's duration. The remainder of his history was irrelevant.

Examination—Physical examination showed a well developed, moderately well nourished middle-aged man with signs of recent loss of weight. His skin was dry, with some loss of elasticity. The pupils were equal and reacted to light and in accommodation. He had a number of carious teeth. His lungs were clear to auscultation and percussion. The heart was of normal size, the sounds were of good quality and the blood pressure was 120 systolic and 70 diastolic. The abdomen was symmetric and soft. In the right upper quadrant there was a large firm mass which was palpable below the edge of the liver. It felt about 5 cm in diameter. It did not move with respiration. Rectal examination gave normal results except for anal spasm and an enlarged soft prostate. His weight on admission was 144 pounds (65.3 Kg). Examination of the blood showed 3,500,000 red blood cells, 62 Gm of hemoglobin, 24 per cent of hematocrit, 11,100 white blood cells and a normal blood smear except for hypochromia. The urine had a specific gravity of 1.020 and gave a negative reaction for albumin, sugar and bile. Blood chemistry determinations showed serum protein 5.8 Gm and nonprotein nitrogen 42 mg per hundred cubic centimeters, blood chlorides of 106.2 milliequivalents per liter, a vitamin C level of 0.2 mg per hundred cubic centimeters and a normal reaction to the van den Bergh test. The stool gave a positive reaction to the guaiac test. A gastric analysis showed some brown-yellow fecal-smelling fluid with no free hydrochloric acid and a negative reaction to the guaiac test. Roentgen examination of the gastrointestinal tract by R. Schatzki showed a normal esophagus and

The duodenal cup was wide. The second and third portions of the duodenum appeared normal but were displaced medialward. Most of the barium after entering the duodenum passed into an irregular cavity with finger-like extensions in the right upper quadrant, and then entered the colon. The findings indicated a duodenocolic fistula and a large mass in the right upper quadrant. The mass had the appearance of a large carcinoma of the hepatic flexure. Examination after a barium enema showed normal filling to the hepatic flexure, where a filling defect of 7 cm was noted. A small amount of barium passed into the first portion of the duodenum. The descending portion of the duodenum appeared uninvolved but there appeared to be some infiltration of the ascending portion of the colon. The findings confirmed the previous roentgenogram in that they showed a large tumor of the hepatic flexure with a fistula into the proximal part of the duodenum.

Operations and Course.—Following his admission two blood transfusions of 500 cc each were given.

On Nov 22, 1941 a peritoneoscopy was done under local anesthesia by Dr E B Benedict. The liver throughout the anterior surface of both lobes appeared of normal color, smooth in outline with a sharp edge. There was no evidence of metastatic disease in the liver or peritoneum. The fundus of the gallbladder appeared normal. The mass in the right upper quadrant was entirely covered by omentum, so that it was impossible to tell regarding the fixation of it.

On November 25, twelve days after admission to the hospital, an operation was performed. The anesthesia was induced with nitrous oxide and oxygen and continued with ether administered through an endotracheal cannula. The abdomen was opened through a left paramedian incision, the rectus muscle being retracted lateralward. The tumor was found to be fairly freely movable, although intimately associated with the duodenum. It seemed unwise to attempt a complete excision at this operation. After it had been determined that there were no metastases in the liver or in the pelvis and that the gallbladder was free and not involved, the stomach was transected at the junction of the middle and lower thirds. The distal end was infolded with two rows of sutures. A posterior Polya anastomosis between the jejunum and the proximal end of the stomach was performed. The transverse mesocolon, through which the jejunum was brought up, was sutured to the wall of the stomach proximal to the anastomosis. The ileum was then transected about 8 inches (20.32 cm) from the ileocecal valve. The distal end of this was infolded with two rows of sutures and dropped back into the peritoneal cavity. An end-to-side anastomosis was performed between the proximal end of the ileum and the transverse colon 6 inches (15.24 cm) distal to the growth. The gastrojejunostomy and the ileocolostomy were carried out according to the Allen² modification of the Parker-Kerr aseptic type of intestinal anastomosis. The abdominal wound was then closed in layers without drainage. The operation required two hours and a half, and during this time the patient received intravenously 1,000 cc. of citrated blood.

The patient made a satisfactory convalescence except for the complication that large amounts of thin fecal material drained from an indwelling nasal catheter which had been placed in his stomach. On the fourth postoperative day this amounted to as much as 4,000 cc.

2. Allen, A W. Aseptic Intestinal Anastomosis Applicable to Gastrojejunocolic Fistula Surgery. 1:338 (March) 1938.

A positive fluid balance was maintained despite this by the use of fluids injected intravenously. He received a transfusion of 500 cc of blood on the third, fifth and eleventh postoperative days. The drainage from his stomach gradually decreased, and on the tenth postoperative day he had a positive fluid balance, so the indwelling nasal catheter was removed.

On December 4, the ninth postoperative day, it was noted that his right leg had become edematous and tender in the calf, and a diagnosis of deep venous thrombosis was made. Accordingly, under local anesthesia the right femoral vein was exposed in the groin. A large clot was removed from it. The vein was ligated and divided between the ligatures. On the following day, the tenth postoperative day, venous thrombosis of the left calf was noted. With the patient under local anesthesia with procaine hydrochloride the

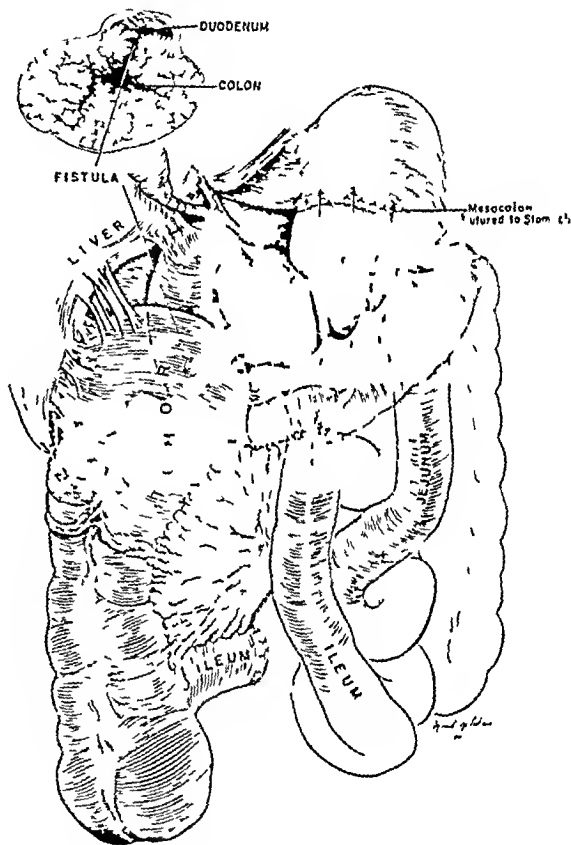


Fig 1—Operative sketch showing the first stage procedure to by-pass the duodenocolic fistula in case 1. The stomach and terminal part of the ileum have been transected. A posterior gastrojejunostomy and an ileo-transverse colostomy distal to the carcinoma have been performed. The distal ends of the stomach and ileum have been closed. The inset shows a cross section through the duodenum and the colon at the site of the fistula.

superficial femoral vein of this extremity was interrupted in the groin. On December 11, fourteen days after his first operation, a second abdominal operation was performed. The anesthesia was induced with nitrous oxide and oxygen and continued with ether administered through an endotracheal cannula. The abdomen was opened through a right paramedian incision, the rectus muscle being retracted lateralward. An additional transverse abdominal incision was made extending lateralward out into the right flank, making a T-shaped incision. The cecum and ascending colon with the terminal ileum attached were first freed up

as for colectomy of the right side. A large amount of inflammatory and carcinomatous tissue was encountered in the right gutter. It was possible to get entirely around this, although it was necessary to sacrifice the right ureter in order to do it. The dissection was continued upward until the duodenum was reached. It was freed from the inferior vena cava posteriorly, which gave off a few small tributaries to it. The distal half of the stomach, the duodenum down to the point where it passes beneath the superior mesenteric vessels, the head of the pancreas, the terminal part of the ileum, the appendix, the cecum, ascending colon and the right portion of the transverse colon with the tumor were removed en masse. The common bile duct was divided as it entered the second portion of the duodenum. The pancreas was resected at the point where the portal vein crosses beneath it. The right colic and ileocolic arteries and veins were ligated at their origins from the superior mesenteric artery and vein. The transverse colon was divided

the renal artery and vein being doubly ligated. The raw area in the right side of the abdomen was peritonealized. The main pancreatic duct was isolated and ligated with a cotton ligature. The cut end of the pancreas was closed with interrupted sutures of cotton. A few glands were noted in the region of the portal vein at its junction with the superior mesenteric vein. This was the only evidence that there might be metastatic disease. The T tube in the common duct was brought out through a small stab wound in the right side of the abdomen. Two cigaret wicks were placed in the region of the sutured end of the pancreas and were separated from the common duct tube by a small amount of gastrohepatic omentum. The abdomen was closed in layers after 4 Gm of sulfanilamide was deposited in the right side. There was no free omentum to use to wall off any of the intestines because it had been involved in the tumor and had to be resected.

The operation lasted five hours and thirty-five minutes, and the patient received two transfusions of citrated blood of 500 cc each. The blood pressure was not discernible at the end of the operation, but his pulse rate was in the neighborhood of 130. Despite the magnitude of the operation and the long time it required to complete it, the patient had a fairly good convalescence. He was placed in an oxygen tent, sulfadiazine was given intravenously. This was continued for three days postoperatively, 4 Gm being given each day. Pancreatic secretion commenced to drain on the fifth postoperative day. By means of suction in the wound this was collected, and it amounted to 500 or 600 cc each day. The fistula gradually stopped draining sixteen days after the operation. On Jan 6, 1942, twenty-six days after the operation, a considerable amount of pus drained through the lateral end of the transverse incision. After this he improved. An injection of hippuran through the common duct tube showed prompt emptying of the contrast material into the jejunum. It was noted about this time that he had definite avitaminosis with a smooth red atrophic tongue. He was given vitamin B parenterally. On January 28, his weight was 125 pounds (56.7 Kg). His serum protein was 4.5 Gm and his nonprotein nitrogen 15 mg per hundred cubic centimeters. He had considerable difficulty in eating, but gradually improved. His wounds finally healed, and he was discharged from the hospital on February 3, fifty-four days after his last operation. He was sent to a nursing home, where he stayed until March 12, at which time it was reported that his appetite was very good, that he had gained weight and that he was able to be up and about.

Pathologic Examination—The pathologist's report was as follows. **Gross Examination**. A kidney weighed 191 Gm and measured 11.5 x 6.5 x 4 cm. The capsule was thin and stripped readily, to reveal a smooth, brownish purple surface. The calices were not dilated, the pelvis was smooth and shiny. The intestinal mass measured 33 x 17 x 18.5 cm. It consisted of a central tumor measuring 15 x 9.5 x 18 cm and located 8 cm above the tip of the cecum. The mass was located primarily within the colon, which was almost completely filled. The tumor was a soft, fungating papillary reddish purple mass, the center of which was grossly necrotic. The remaining mucosa of the colon was normal in appearance. Attached to the cecum were a normal-appearing appendix measuring 6 x 0.8 cm, and a normal-appearing section of the ileum measuring 14 cm, the end of which had been previously sutured. The tumor had extended through the wall of the colon to invade the wall of the duodenum.

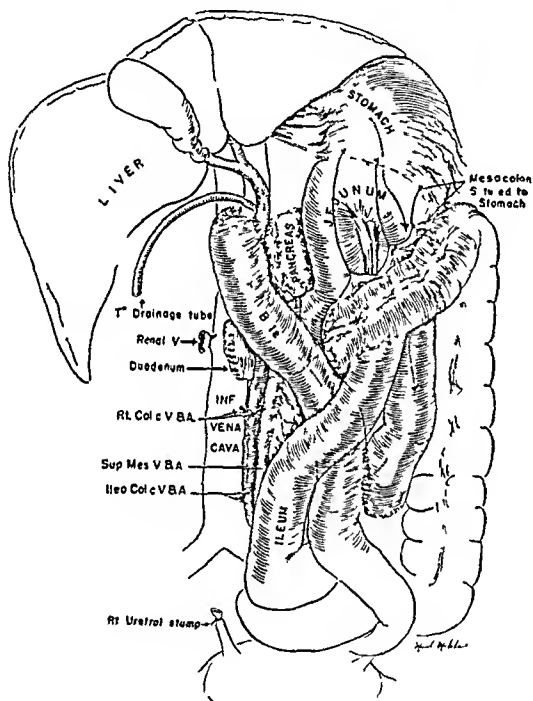


Fig 2—Operative sketch showing the complete second stage procedure after removal of the carcinoma and the organs involved in case 1. In this patient the right kidney also was removed. The choledochojejunostomy over a T tube and the jejunojunction after the principle of Roux are shown.

just proximal to the ileotransverse colostomy. The distal end of the third portion of the duodenum and the colon were infolded with two layers of sutures. The flow of bile into the intestine was reestablished by the Roux type of anastomosis as recommended by Whipple.¹ The jejunum was divided about 12 inches (30.48 cm) distal to the gastrojejunostomy. A choledochojejunostomy was performed between the distal end of the jejunum and the end of the common bile duct. This was made over a T tube to give the bile a vent and also to prevent temporary closure of the anastomosis from edema. A side-to-side jejunojunction was made between the proximal jejunal segment, after the end of it was closed, and the jejunum distal to the choledochojejunostomy. Since the right ureter had to be sacrificed, the right kidney was then removed.

which was affixed to the upper outer aspect of the colon. The tumor extended into the duodenum over an area measuring 10 x 5 cm and protruded into the lumen for a distance of about 1.5 cm. There was a fistulous communication through the necrotic tumor between these two structures. The tumor apparently had also grown into the omentum, where it was found as firm, gray-white strands of tissue infiltrating the soft, fatty tissue. The stomach portion measured 11 x 9 cm and showed soft thick folds and had been previously sutured at its proximal end. The tissues examined consisted of colon, ileum, kidney, stomach, appendix and duodenum. There was a portion of the pancreas on the posterior aspect of the tumor mass which was intimately adherent to it and the duodenum and partially infiltrated with the tumor tissue.

The diagnosis was adenocarcinoma, grade 2, of the transverse colon with perforation into the duodenum, normal kidney, normal appendix.

The patient reported to the hospital on August 17, stating that he had felt well until three weeks previously when he began to have indigestion immediately after eating, with pain in the epigastrium and occasional vomiting and five to six stools a day. These consisted mostly of undigested food. He was readmitted to the hospital for study and a roentgenogram of the gastrointestinal tract was made. This showed a subtotal gastrectomy with prompt emptying of the barium into the anastomosed jejunum. The upper part of the jejunum was slightly dilated and no barium passed it during forty-five minutes. The findings were those of a partial obstruction in the upper part of the small intestine. Blood chemistry studies at this time showed a nonprotein nitrogen of 20 mg and serum protein of 4.8 Gm per hundred cubic centimeters and blood chlorides of 103.2 milliequivalents per liter. An enema of barium sulfate was given at this time, and it showed that the barium passed from the rectum to the midtransverse colon. Just proximal to the splenic flexure the barium was observed to go into the small intestine at the site of the anastomosis. No evidence of recurrent disease was observed. The red blood count was 4,300,000, the white blood count 8,200 and the hemoglobin content 80 per cent. He was discharged from the hospital five days after his admission on August 22. He was given instructions in the regulation of his dietary regimen to reduce the amount of muscle, vomiting and diarrhea and to correct his vitamin deficiency. His weight on this admission was 141 pounds (64 Kg) a gain of 16 pounds (7.3 Kg) since his discharge from the hospital.

One month later he died at another hospital, where a diagnosis of heart failure was made. No autopsy was performed, so it is impossible to determine if metastases had developed which might have played a role in his death. He had survived ten months since the tumor had been resected.

CASE 2—History.—H. W. R., a 45 year old man, American, a bricklayer, was admitted to the Massachusetts General Hospital on Jan. 4, 1943. The chief complaint was shifting pain in the epigastrium and in both lower quadrants of the abdomen for the past seven months. The pain was described as constant dull and aching with transient sharp epigastric exacerbation which sometimes were referred to the back. His appetite was poor and occasionally he felt nauseated and vomited. There was no relation between the pain and his meals, there was no change in bowel habits except for a slight watery brown diarrhea in the past week. He had gradually lost strength and in the past four months had lost 23 pounds (10.4

Kg). In July 1938 it was found that he had a positive reaction to the Wassermann and Hinton tests at the Peter Bent Brigham Hospital. He then received treatment for syphilis both at that hospital and at the Massachusetts General Hospital. This type of therapy resulted in attacks of dermatitis, but it was possible to continue antisyphilitic treatment by careful regulation of the dosage. In March 1941 he complained of precordial pain, radiating down his left arm, and a diagnosis of a recent anterior myocardial infarction was made by electrocardiogram. This condition responded well to rest and regulation of his activities.

Examination.—Physical examination showed a well developed, fairly well nourished, pale, sallow man 45 years old, who appeared chronically ill and showed evidence of recent loss of weight. His skin was pale and dry, with hyperkeratotic lesions and scaling of the skin of the forearm. There was a slight yellowish tinge to the scleras of his eyes. The right pupil was slightly larger than the left. Both pupils reacted to light and in accommodation. His heart was not enlarged to percussion, the sounds were distant and muffled. The rate and rhythm were regular. The blood pressure was 112 systolic and 60 diastolic. The lungs were clear to percussion and auscultation. Abdominal examination revealed in the right upper quadrant a large mass just below the costal margin, which was felt to be an enlarged liver. It extended down into the right flank below the level of the umbilicus. It descended slightly on respiration. The edge of this mass was not readily palpable, it was slightly tender on pressure. Rectal examination gave normal results. Examination of the blood showed 4,400,000 red blood cells, 12.5 Gm of hemoglobin, 15,300 white blood cells and a normal blood smear. The urine had a specific gravity of 1.016 and gave a negative reaction for albumin, sugar and sediment. Repeated examinations of the stools showed strongly positive reactions to the guaiac test for blood. Blood chemistry determinations showed a serum protein of 5.7 Gm, nonprotein nitrogen of 26 mg, albumin of 2.9 Gm and globulin of 2.8 Gm per hundred cubic centimeters. The prothrombin time was twenty-three seconds with a normal of twenty-two seconds. The reaction to the van den Bergh test was normal. The blood chlorides were 98.3 milliequivalents per liter. The blood hematocrit was 38.8 per cent. Roentgen studies by Dr. R. Schatzki after the patient was given dye revealed a normal gallbladder. An intravenous pyelogram revealed normal kidneys. A series of gastrointestinal roentgenograms after barium was given by mouth showed a scarred deformity of the duodenal cap. The junction of the second and third portions of the duodenum as well as the lower third was poorly filled throughout the examination. The third portion of the duodenum appeared to be irregular and was probably ulcerated. The examination was suggestive of an ulcerating tumor of the third portion of the duodenum. The esophagus and stomach were normal. A barium enema flowed easily up to the junction of the hepatic flexure with the transverse colon. At this point the barium column first met an obstruction and then filled an irregular pocket, then it entered the duodenum at the junction of the second and third parts. Later films showed the stomach and jejunum partially outlined by barium.

A diagnosis was made of a duodenocolic fistula with marked destruction of the wall of the colon, probably secondary to carcinoma of the colon.

Operations and Course.—The patient's condition did not improve during these studies. On January 23, his red blood count had dropped to 2,000,000. He received

transfusion of 500 cc of citrated blood on January 23 and 24. On the evening of January 24, severe pain suddenly developed in the right upper quadrant of the abdomen, with spasm and tenderness in the region of the mass. His temperature had risen to 103 F. The development of these signs and symptoms indicated beginning peritonitis, possibly from perforation of the neoplastic growth.

An emergency laparotomy was performed on January 24, at 10 o'clock in the evening. The anesthesia

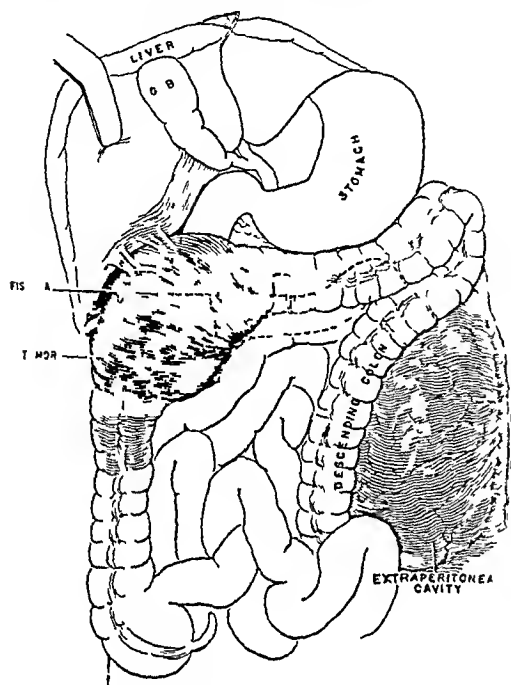


Fig 3—Operative sketch of the carcinoma and the peritoneal cavity found in case 2 are shown. Note the descending colon lies medial to the latter.

was induced by nitrous oxide and oxygen and controlled with ether administered through an endotracheal tube. The abdomen was opened through a left paramedian incision, the rectus muscle being retracted lateralward. The lesion in the right side of the colon was visualized. It was covered with fresh fibrin but there was no active peritonitis. It was ascertained that there were no metastatic nodules in the liver. The large tumor mass was slightly movable, and it was considered to be an operable growth. The stomach was transected through its midportion. An antecolic gastrojejunostomy was performed with the distal loop attached to the greater curvature. A congenital anomaly was encountered when the upper part of the jejunum was searched for. The ligament of Treitz could not be found, and then it was ascertained that the upper loops of jejunum lay in a separate peritoneal cavity which was lateral to the attachment of the mesentery of the descending colon (fig 3). This sac which contained the upper several feet of jejunum, was anteriorly and the ligament of Treitz localized the aperture in the sac was made as large as possible to prevent strangulation of the bowel. The gastrojejunostomy was performed approximately 12 inches (30-48 cm) distal to the ligament of Treitz. An antecolic type of anastomosis was performed. Because of the displacement of the descending colon medialward in the congenital anomaly, it was necessary to bring the loop of jejunum over both the transverse colon and

the proximal portion of the descending colon (fig 4). The terminal ileum was next divided about 6 inches (15 cm) proximal to the ileocecal valve and an end-to-side aseptic type of anastomosis was performed between the proximal end of the ileum and the transverse colon about 8 inches (20 cm) distal to the growth. The distal end of the ileum was closed with two rows of sutures and dropped back into the peritoneal cavity. Both the gastrojejunostomy and the ileocolostomy were carried out according to the Allen² modification of the Parker-Kerr technic. The abdominal wound was then closed in layers without drainage. The patient received one transfusion of 500 cc of citrated blood during the operation and another one immediately afterward. Because of danger of peritonitis administration of sulfadiazine intravenously was begun.

Following this operation the patient did fairly well but large amounts of thin brownish fecal-smelling fluid drained from a Levine tube placed in his stomach. Despite keeping this tube on constant suction he retched and vomited considerably and on January 31, seven days after his operation, dehiscence of the wound developed. He was taken to the operating room, and under spinal anesthesia the wound was sutured with silver wire through all layers of the abdominal wall. At this operation it was ascertained that the gastrojejunostomy appeared in excellent condition and was patent. The distal loop of the jejunum was dilated about 8 inches distal to the anastomosis, but there was no obvious mechanical obstruction. It was decided at this time to do a supplementary jejunostomy for feeding purposes since the gastrojejunostomy was not functioning, as recommended by Allen³. This was done by suturing a rubber catheter into the jejunum with

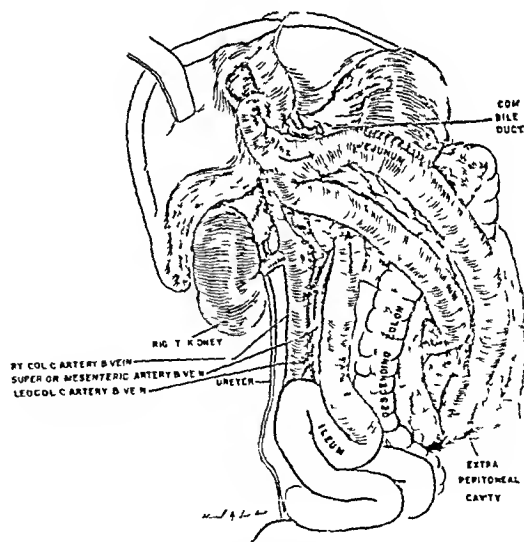


Fig 4—Operative sketch showing the completed second stage procedure after removal of the carcinoma and the organs involved in case 2. The cholecystojejunostomy proximal to the gastrojejunostomy is shown. Note the latter is an antecolic type over both transverse and descending colons which was necessary due to the congenital anomaly of an extraperitoneal cavity.

two purse-string sutures bringing the tube out through a stab wound in the left hypochondrium.

3 Allen, A. W., and Welch, C. E. Jejunostomy for the Relief of Malfunctioning Gastro-Enterotomy Stoma. *Surgery* 9:163 (Feb) 1941.

The most satisfactory jejunostomy feeding was equal parts of milk and lime water. He was given 1,000 cc of this mixture each day, and to it was added 100 Gm of amigen⁴ as a 10 per cent solution and vitamins B, C and K. Large amounts of material continued to drain from his stomach tube. This was strained and also run into his jejunostomy tube by a continuous drip. The gastrojejunostomy gradually began to function, and it was possible to feed him small amounts of liquid food by mouth. By means of this regimen it was possible to keep his blood chemistry practically normal. On February 12, his nonprotein nitrogen was 20 mg and his serum protein 6.3 Gm per hundred cubic centimeters, and his blood chlorides 93.8 milliequivalents per liter.

On February 4, eleven days after his first operation and four days after the suture of his wound, pain developed in the chest and a roentgenogram showed a shadow at the base of the right lung consistent with a pulmonary infarct. For this reason and because of slight tenderness in the calves of his legs he was taken to the operating room again and under local anesthesia with procaine hydrochloride both superficial femoral veins were interrupted in the groin just distal to the profunda branch to prevent further embolism.

After about two weeks of the jejunostomy feedings it was decided that he was in as good a condition as possible and on February 20, twenty-seven days after his first laparotomy, the tumor mass was removed through a transverse abdominal incision. Endotracheal ether anesthesia was used. Numerous peritoneal adhesions were encountered, involving the small bowel. These had developed since the resuture of the wound. The terminal ileum, appendix, cecum and ascending colon were first freed up as for colectomy on the right side. Then the distal portion of the stomach, the duodenum and the tumor mass were freed up from the posterior abdominal wall. The common bile duct was normal in size and was severed near its junction to the duodenum. The pancreas was resected through the neck. The duodenum was divided in its third portion, and the transverse colon was divided well distal to the carcinoma but proximal to the ileotransverse colostomy. An attempt was made to free up the distal portion of the duodenum to bring it around to anastomose with the gallbladder. This was impossible because of the numerous adhesions and the congenital anomaly noted at the first operation, so the distal end of the duodenum was closed with two rows of sutures. The distal end of the colon was treated in a similar manner. The common bile duct was of normal size or smaller, so it was tied and a cholecystojejunostomy was performed between the gallbladder and the jejunum proximal to the gastrojejunostomy. The pancreatic duct was ligated with cotton and the cut end of the pancreas sutured with interrupted sutures or cotton. The abdominal wound was closed in layers and two cigaret wicks were brought out through a stab wound in the right flank. Four grams of sulfanilamide powder were placed in the raw area from which the tumor had been removed. The operation lasted four hours and forty-five minutes. The patient received three blood transfusions of 500 cc each during the operation and immediately after the operation received an additional 1,000 cc. of blood, totaling in all 2,500 cc. Despite the extensive dissection and the long operation

he stood the procedure very well. He was placed in an oxygen tent for two days. Administration of sulfadiazine intravenously was commenced the day of operation. He was given another blood transfusion on February 22, the second postoperative day, and one on February 23, of 500 cc each.

His convalescence was complicated the first five postoperative days by jaundice. His reaction to the van den Bergh test rose to 20.2 mg of bilirubin on the third postoperative day, but it returned to normal on the ninth postoperative day. It was felt that the jaundice was secondary to intensive chemotherapy and the intraperitoneal use of sulfanilamide at the time of the operation. Within a few days after the removal of the large tumor mass and the organs it involved, his gastrointestinal tract began to function normally and although feedings were continued for a time through the jejunostomy tube he was able to take nourishment by mouth on the fifth postoperative day. The oral feedings were gradually decreased so that on the eighth postoperative day he was taking a soft solid diet. A moderate amount of pancreatic juice drained through the sinus in his right flank, but it never was a serious problem. He was discharged from the hospital on March 19, fifty-four days after his first operation and twenty-seven days after his second operation. He was able to take a six meal bland diet without discomfort. He was given iron, vitamin B concentrate and vitamin C and a request to the ration board for more points in order to obtain a better diet for regaining his weight.

The pathologist's report was as follows. Gross Examination. There was a normal-appearing terminal ileum, including the ileocecal valve, measuring 12 cm in length. The proximal end had been previously closed and was healing well. Attached to a grossly normal cecum was a normal-appearing appendix, measuring 5.5 cm in length. Beginning 20 cm from the ileocecal valve was a constriction caused by a gray-white granular ulcerating mass 8 cm in length with raised edges not covered with mucosa. Beyond the tumor was 6 cm of normal transverse colon ending as an infolded stump. The mass had eroded posteriorly and superiorly through the wall of the colon, invading and ulcerating into the anteroinferior wall of the duodenum, forming a fistula 4 cm in diameter. A portion of the stomach measuring 8 cm along the lesser curvature and 12 cm along the greater curvature and having the proximal end closed and fairly well healed was attached to 4 cm of apparently normal duodenum before it entered the mass. Distal to the fistula there was 6 cm of normal duodenum. Entering the duodenum in the uninvolved portion beneath the mass was a common bile duct which was normal and measured 4 cm. Beneath the duct and beneath the mass was the head of the pancreas measuring 4 by 4 by 3 cm. It was normal. Many enlarged lymph nodes varying in size from 0.5 to 3 cm contained firm gray-white tumor-like tissue. Submitted separately were several soft gray-red lymph nodes, each measuring 1 cm in diameter.

The diagnosis was carcinoma of the transverse colon with invasion of the duodenum, duodenocolic fistula, chronic gastritis and normal pancreas.

The microscopic examination showed that the regional lymph nodes were negative and the tumor was undifferentiated.

The patient was seen on October 20, eight months after his tumor had been removed. He was able to work but was having some abdominal discomfort and cramps. Examination of his abdomen revealed a firm movable mass in the right lower quadrant which was thought to represent metastatic disease.

⁴ A sterilized aqueous, nonpyrogenic 10 per cent solution of an enzymic hydrolysate of purified casein and pork pancreas. Hydrogen ion concentration is adjusted to pH 6.5 (Mead Johnson & Company).

COMMENT

Carcinoma of the colon is a relatively common disease. If it is located in the right half of the transverse colon it may erode into the duodenum to produce a duodenocolic fistula. An adequate operation to cure malignant disease should include the removal of the primary tumor, any organ involved by it, and the regional lymph nodes. In cases similar to the two presented, it is necessary therefore to plan a "block" type of resection which will remove the distal half of the stomach, the duodenum, the head of the pancreas, the terminal ileum, the cecum, the ascending colon and the right half of the transverse colon. Patients with lesions of this type are in a poor nutritional state because of the malignant disease and their inability to assimilate nourishment, the result of the high intestinal fistula.

An operation of the magnitude outlined requires multiple anastomoses to reestablish gastrointestinal and biliary continuity and in addition an extensive dissection in the retroperitoneal area. If it is attempted as a one stage procedure with the patient in a poor nutritional state, there is grave danger of uncontrollable surgical shock. In addition sepsis may be a serious complication since all the lumens of the bowel, which it is necessary to cut across to do the resection and utilize in the various anastomoses, namely, the stomach, duodenum, jejunum and colon, contain highly infective fecal material, the result of the duodenocolic fistula. For these reasons the operative procedure in both cases was divided into two stages.

The first stage consisted in by-passing the duodenocolic fistula in order to improve the patient's condition and to free the upper intestinal tract of fecal material (fig 1). This was done by transecting the stomach and the ileum and then performing a gastrojejunostomy and an end-to-side ileotransverse colostomy as far distal to the growth as possible. The stomach was divided at the junction of its middle and lower thirds and the ileum 6 inches (15.24 cm) proximal to the ileocecal valve. The distal end of the stomach and ileum were closed and dropped back into the peritoneal cavity. In one case a retrocolic gastrojejunostomy was performed, while in the other an antecolic gastrojejunostomy was necessary because of a congenital anomaly of the peritoneal cavity involving the upper part of the jejunum (fig 3). The former is preferable since the ileotransverse colostomy and the jejunal anastomosis to the biliary tract can be more readily accomplished if the jejunum does not cross anterior to the transverse colon.

Large amounts of liquid fecal material drained from the stomach in both cases following the first stage operation. This apparently resulted from a reflux of ileal contents from the ileotransverse colostomy into the transverse colon through the fistula into the duodenum and then into the stomach through the gastrojejunostomy. This complication hindered the preparation of the patients for the second stage procedure. In the first case the fecal gastric drainage stopped after a week, but in the second one it persisted for a longer period. It could have been avoided if the transverse colon had been divided proximal to the ileotransverse colostomy at the first stage operation. It was intentionally omitted, however, because it was feared that material might collect under tension in the right part of the colon, since the only opening in it would have been the fistulous tract into the duodenum. In view of the postoperative course in these 2 patients it seems that division of the transverse colon proximal to the ileotransverse colostomy could be carried out safely with benefit at the first operation in patients with similar lesions, since the duodenocolic fistula will give an adequate vent to the closed off part of the colon on the right side.

The gastrojejunostomy in the second case did not function properly after the first stage operation. The cause of this was not determined. It may have resulted from some reflex mechanism secondary to the primary growth, since after the second stage it functioned properly. In order to prepare this patient for the second operation it was necessary to perform a jejunostomy for feeding purposes. The value of this simple procedure cannot be overemphasized under these circumstances, as Allen³ has pointed out. There is no question that if it had not been done in this patient he would never have been in a condition to withstand the radical second stage operation. Equal parts of milk and lime water proved to be the best jejunostomy formula. To each liter of this mixture were added 100 Gm of amigen as a 10 per cent solution and vitamins B, C and K. In addition the drainage from the stomach was filtered and run into the jejunostomy opening by a Murphy drip. He was kept on this regimen for eighteen days prior to the second stage operation. The most striking result obtained by this therapy was the increase of his serum protein level from 4 to 6.3 per cent and in addition normal chloride and nonprotein nitrogen levels were maintained in the blood.

The second stage was performed in the first patient fourteen days after the first stage and in the second patient after eighteen days. The operative procedure in both cases necessitated

the removal of the distal portion of the stomach, the duodenum, the head of the pancreas, the terminal ileum, the cecum, the ascending colon and half of the transverse colon with the tumor mass (figs 2 and 4). In the first case nephrectomy was performed on the right side in addition, since the right ureter had to be sacrificed because of its apparent involvement in the tumor mass.

The terminal part of the ileum, the cecum and ascending colon were dissected free as in a colectomy of the right portion. A radical resection of the ileocolic mesentery was done in order to remove the regional lymph nodes. The ileocolic and right colic arteries and veins were divided and ligated at their origins from the superior mesenteric artery and vein. The middle colic artery and vein with their left branches were preserved to supply the region of the ileotransverse colostomy. The right branch of these vessels was sacrificed so that additional transverse mesocolon and lymph nodes could be resected. The distal end of the stomach, the duodenum and the head of the pancreas were mobilized in this order. Since the beginning of the third portion of the duodenum lies directly on the inferior vena cava, extreme care was taken not to damage this large vessel. A number of small veins connecting the two structures were carefully ligated and divided. The resection of the duodenum was carried to the point where the superior mesenteric vessels cross it. After it was divided between clamps the distal end was closed with two rows of sutures.

The head of the pancreas was mobilized with the duodenum, and it was resected at its junction with the body. This exposed the portal vein at its origin, formed by the junction of the splenic and superior mesenteric veins. These vessels were preserved with the utmost care, since ligation of the portal vein will rapidly produce death. The pancreatic duct was isolated in both cases and ligated with a fine cotton ligature. The dissection as described permitted the removal en masse of the tumor with the distal half of the stomach, the duodenum, the head of the pancreas, the terminal ileum, the cecum, the ascending colon, the right half of the transverse colon and the attached ileocolic and transverse mesocolons.

The common bile duct in both cases was divided near the upper border of the first portion of the duodenum. The method of reestablishment of the biliary circulation into the intestine was different in the 2 cases. A choledochojejunostomy with a jejunojejunostomy distal to the gastrojejunostomy after the method of Roux

as advised by Whipple,^{4a} was performed in the first case. This was feasible because the common bile duct was considerably dilated. The choledochojejunostomy was performed around a T tube, a step which furnished a safety valve and at the same time prevented temporary blockage of the anastomosis by edema (fig 2). In the second case the duct was too small to make a satisfactory anastomosis to the jejunum. Accordingly a cholecystojejunostomy was performed. In order to simplify the anastomosis it was carried out between the gallbladder and the jejunum proximal to the gastrojejunostomy. The gallbladder was mobilized by freeing the fundus of it from the liver bed (fig 4). This was necessary in order to make the anastomosis without tension on the suture line. An attempt in this case was made to mobilize the distal portion of the duodenum to anastomose it to the gallbladder, as described by Dennis⁵ and Pearse,⁶ but this was impossible because of a congenital anomaly involving the upper part of the jejunum. Both types of anastomoses used in these patients functioned satisfactorily, but the type in the second case seems preferable since it is less complicated, requiring only one anastomosis and at the same time giving protection against the regurgitation of intestinal contents into the biliary tract, similar to the Roux type of anastomosis. In addition bile enters the intestinal tract proximal to the gastrojejunostomy, so that the acid gastric juice is neutralized, with the result that there is the relatively less danger of the development of gastrojejunal or jejunal ulceration.

The severed end of the pancreas in both cases was sutured with interrupted mattress sutures of fine cotton after the main pancreatic duct was ligated with the same material. The raw area resulting from the removal of the organs was peritonealized as much as possible in order to prevent the small intestine from becoming adherent to it and producing intestinal obstruction. The abdominal cavity in both cases was drained with gauze wicks surrounded with rubber tubing. These drains were placed posterior to the new peritoneal floor and brought out through stab wounds in the right flank. This method gave dependent drainage with 1

4a Whipple, A. O. Present Day Surgery of the Pancreas, *New England J. Med.* 226:515 (March) 1942.

5 Dennis, C. A Modified Whipple Operation for Carcinoma of the Head of the Pancreas. *Surgery* 201 (Aug.) 1942.

6 Pearse, H. E. A Simplified Anastomosis after Resection of the Duodenum and Head of the Pancreas. *Surg., Gynec. & Obst.* 75:333 (Sept.) 1942.

chance of puddling and secondary infection. It also permitted the suturing of the main abdominal wound intact and prevented the profuse drainage, which so often occurs in this type of case, from interfering with the healing of it, an extremely important consideration since wound disruption is most apt to occur in patients who are in as poor a state of nutrition as these were.

In both cases large amounts of pancreatic secretions drained for about four weeks, after which the drainage ceased. Neither patient appeared to suffer greatly from the loss of the external secretion of the pancreas, but it is believed that some type of pancreojejunal anastomosis is desirable in resections of this type. It is possible that in both cases spontaneous internal pancreojejunal fistulas developed, which would best explain the cessation of the drainage.

The type of incisions used requires special attention since it is important to have as few peritoneal adhesions as possible in the operative field at the second operation, to facilitate the extensive resection that must be carried out. Accordingly at the first stage a left paramedian incision was used which permitted adequate exposure for determining the operability of the main lesion and, at the same time, the carrying out of the gastrojejunostomy and the ileotransverse colostomy without disturbing the peritoneal cavity to the right of the midline, where the dissection must be done for the second stage. The use of a transverse incision for the second stage extending well out into the right flank and across the midline to the left permitted the dissection to be done posteriorly with greater ease than if a vertical incision had been employed.

Extensive surgical procedures, such as the second stage operation performed on these patients, are likely to be accompanied by surgical shock. This results from the extensive dissection in the splanchnic area, the loss of moderately large amounts of blood and the prolonged anesthesia. The most effective way to combat surgical shock is the maintenance of an effective volume of blood by multiple transfusions. The first patient received one transfusion of 500 cc before the first stage procedure and six between this operation and the second stage over a period of sixteen days. During the second operation he was given two transfusions and an additional two postoperatively the same day, a total of 2,000 cc of blood. The next day he received another 1,000 cc and during the remainder of his convalescence he was given two more transfusions of 500 cc, each in an attempt to raise

the serum protein level. This patient received a total of fifteen transfusions of 500 cc, or a total of 7,500 cc of blood. The second patient received two transfusions of 500 cc before the first stage procedure and two more the day it was performed. This large amount was given because his red blood count was 2,000,000 before the operation. After the four transfusions it rose to 3,500,000. Between the two stages he received five additional transfusions. During the second stage operation three transfusions were given, then two additional ones postoperatively on the same day, so that he received a total of 2,500 cc of blood during that day. At the end of the first two and one-half hours of the operation his blood pressure had fallen from 130 systolic and 90 diastolic to 75 systolic and 50 diastolic, and his pulse rate had risen from 90 to 132. At the end of the five hour operation the blood pressure had risen to 100 systolic and 60 diastolic, and the pulse rate had dropped to 112, showing the beneficial effect of a transfusion of 1,500 cc of blood. With the two additional postoperative transfusions his blood pressure rose and maintained a level of 125 systolic and 80 diastolic with a pulse rate of 110. During his postoperative convalescence he received three additional transfusions. This patient received a total of seventeen transfusions of 500 cc, or a total of 8,500 cc, of blood.

When planning such extensive surgical operations as these patients were subjected to, it is of prime importance to have available large amounts of blood for multiple transfusions. Without this precaution surgical shock will develop, from which patients will succumb even though a technically perfect operation has been performed. The modern blood bank with facilities for the storage of blood, established in many of the large hospitals, makes available these large quantities of blood on short notice, which was not possible when the older method of transfusion was used by drawing the blood from the donor when it was needed. Once surgical shock has developed and persisted for several hours, it may represent an irreversible reaction whereas by the early administration of transfusions it may be possible to prevent its development. The administration of large transfusions in one case 1,000 cc and in the other 1,500 cc, during the course of the operation is emphasized especially as a method to prevent severe or fatal shock, since by this means an effective volume of blood is maintained during the critical period when all the factors of anesthesia, trauma of the operation and loss of blood are acting to produce shock. The use of multiple transfusions before and after the operations also is important.

in order to improve the patient's condition by correcting anemia and aiding in the maintenance of or increasing the serum protein level

Both patients were placed in an oxygen tent for forty-eight hours postoperatively to prevent anoxia, which if present would contribute to shock. Proper fluid and electrolyte balance was maintained with solutions given by the intravenous route containing 5 per cent dextrose in isotonic saline solution and 5 per cent dextrose in distilled water, so that a urinary output of at least 1,000 cc was obtained. To these solutions vitamins B, C and K were added in the form and amount respectively of 50 mg of thiamine chloride, 1 Gm of cevitamic acid and 4 mg of water-soluble vitamin K. For the second patient after the jejunostomy these substances were mixed with the jejunostomy feedings, since they could be given more readily and in less expensive form. In order to build up this patient's serum protein amigen was given intravenously until the jejunostomy functioned and then it was given by this route.

Serious postoperative infection did not develop in either case. It is believed that the local use of sulfanilamide intraperitoneally at the time the tumor was resected and the postoperative intravenous administration of sulfadiazine played an important part in preventing this complication. A sulfadiazine level of 8 to 10 mg per hundred cubic centimeters of blood was maintained postoperatively for a week and then the drug was discontinued. Jaundice developed postoperatively in the second case. It is believed this was the result of combining the use of intraperitoneal administration of sulfanilamide and intravenous administration of sulfadiazine in a patient with a poor liver reserve, since the sulfanilamide is picked up rapidly by the portal system, so that the sulfonamide level in the portal blood is undoubtedly much higher than in the systemic blood and may be of sufficient concentration to produce a toxic hepatitis, especially if sulfadiazine is given concomitantly, as occurred in this patient. For this reason it is now considered preferable to use only sulfadiazine administered by the intravenous route, or if sulfanilamide is used intraperitoneally sulfadiazine therapy should not be commenced until the first postoperative day.

Deep venous thrombosis of the legs is a postoperative complication seen frequently in patients following abdominal operations for a malignant disease. The condition is a serious threat to life from fatal pulmonary embolism. In each of the patients reported on this condition developed in both legs following the first stage operation. In order to prevent pulmonary em-

bolism, bilateral interruption of the femoral veins in the groins was performed with the patient under local procaine hydrochloride infiltration anesthesia as soon as the diagnosis of phlebotrombosis was made, as advocated by Allen et al.⁷ Despite the fact that the extensive second stage operations were carried out following the occurrence of this complication, signs of pulmonary embolism did not develop in either patient after interruption of the femoral vein. It would seem justifiable in similar cases to advocate prophylactic interruption of the femoral veins during the first stage operation or shortly thereafter.

SUMMARY

The surgical extirpation of carcinoma of the right side of the colon, producing a duodenocolic fistula, requires resection of the distal portion of the stomach, the duodenum, the head of the pancreas, the terminal ileum, the ascending colon and the proximal half of the transverse colon.

It is advisable to divide the operative procedure into two stages, since patients with this lesion are in a poor nutritional state, the result of carcinoma and a high intestinal fistula and because highly infectious fecal material is present in all the lumens of the bowel which it is necessary to transect. The first stage consists of transection of the stomach and ileum and the formation of a gastrojejunostomy and an ileotransverse colostomy to by-pass the duodenocolic fistula. The second stage consists of a block extirpation of the primal growth with the involved organs. This necessitates colectomy on the right side and in addition the resection of the organs which it is necessary to remove in performing a Whipple type of operation for carcinoma in the head of the pancreas.

The successful outcome of this major operation, in addition to the technical details, depends first, on adequate preoperative preparation of the patient, second, on the care of the patient during the operation, including the type of anesthesia and the prevention of shock, and third, on the postoperative measures to prevent shock and infection and to maintain an adequate fluid and electrolyte balance. In the preoperative preparation anemia should be corrected with blood transfusions, a low serum protein level should be elevated by transfusions and intravenous administration of amino acids, and in some cases jejunostomy should be performed for feeding purposes, avitaminosis should be corrected by the parenteral and oral administration of vitamins B, C and K.

7 Allen, A. W., Jinton, R. R. and Donaldson, G. A. Thrombosis and Embolism. *Ann Surg* **118**: 728 (Oct.) 1943.

The care of the patient during the operation should include the selection of a safe and satisfactory anesthetic. Since the operations require several hours, ether administered through an endotracheal tube fulfils the necessary requirements and permits in addition the administration of oxygen during the operation. Surgical shock should be prevented by massive blood transfusions.

In the immediate postoperative period additional transfusions are necessary to prevent shock. The use of an oxygen tent in this critical period to prevent anoxia is an important adjunct in treatment. The intravenous administration of

sulfadiazine to combat postoperative infection should be used. Fluids, dextrose and electrolytes should be given in sufficient quantities to maintain a daily urinary output of 100 cc.

Phlebothrombosis of the lower extremities with the danger of pulmonary embolism is a common complication in patients with abdominal carcinoma requiring such major procedures. Fatal pulmonary embolism can be prevented, if this complication develops, by interruption of the femoral vein on both sides. It is suggested that this procedure may be carried out as a prophylactic measure at the first stage operation.

MEDIASTINAL GANGLIONEUROMA

HOWARD K. GRAY, M.D., DUNCAN V. SHEPARD, M.D.,
AND MALCOLM B. DOCKERTY, M.D.C.M.*

ROCHESTER, MINN.

The division of the mediastinal space into three compartments is a delineation which serves more than its originally pure anatomic purpose. Tumors arising in each of these spaces bear certain marks of distinction which permit of their general classification according to situation. Thus the anterior mediastinum is the site of election for dermoid and thymoma. The middle mediastinum is the site of bronchogenic carcinoma and lymphosarcoma. From the structures of the posterior mediastinum arise lymphosarcoma and neoplasms such as neurofibroma and ganglioneuroma whose origin may broadly be considered under the term "neurogenic." Neurofibroma is a relatively common tumor, ganglioneuroma, although somewhat of a curiosity, is important from the standpoints of etiology, diagnosis and prognosis.

Although Knoebell¹ in 1846 reported the first "ganglioneuroma," in the case of "neuroma" reported by Odier in 1803 the lesion undoubtedly was a ganglion cell tumor. It was early recognized that ganglioneuroma can arise from elements within the central nervous system, the peripheral nervous system, the sympathetic and parasympathetic systems and the medullary portion of the suprarenal gland.² The majority of the tumors, however, appear to originate within the sympathetic chains and therefore usually are situated in the cervical region, the posterior mediastinum, the posterior wall of the abdomen or the posterior aspect of the pelvis. These tumors are often multiple and sometimes occur in conjunction with other tumors of nervous origin.² Mediastinal ganglioneuroma is rare, but in the

last twenty-five years, with exploratory thoracotomy becoming more and more common, this tumor has been reported more frequently.³

Bohrer and Lincoln⁴ expressed the opinion that this tumor is rare among children, but in most of the reported cases the patients have been less than 30 years of age. No difference in the incidence in the two sexes has been noted. Bigler and Hoyne,⁵ as well as other authors, found that as a general rule the more advanced the patient's age the greater is the likelihood of the tumor to be benign. As pure ganglioneuroma is usually benign one would expect that it would occur rarely among children.

CLINICAL PICTURE

Many authors stress the absence of symptoms and cases have been reported in which a mediastinal ganglioneuroma had been present eighteen to twenty years without causing symptoms. At times the tumor is first discovered when routine roentgenograms of the thorax are made. In many cases, however, there are symptoms that are referable to the tumor, and a careful inquiry reveals that the symptoms in question have been present for months or years. The symptoms are often ingravescent. Ganglioneuroma does not invade the blood vessels, lymphatics or contiguous structures, but produces symptoms by pressure on the adjacent vessels and organs. Pressure on the trachea may cause a persistent cough, dyspnea and even stridor.

3 Allison, P. R., and Carmichael, R. A. Mediastinal Ganglioneuroma, *Brit J Surg* 27 141 (July) 1939. Cooley, L. E., and McNamara, F. Intrathoracic Ganglioneuroma, *J Iowa M Soc* 117-120 (March) 1940. Harvey, W. C. Ganglionic Neuroma of the Mediastinum in a Child Aged Nine, *Lancet* 1 405-406 (Feb 22) 1930. C. Neuroma, Cabot Case 24422, *New England J Med* 620-623 (Oct 20) 1938. Rosenson, W. Neoplasms of the Mediastinum in Infancy and Childhood. Report of a Case of Ganglioneuroma of the Mediastinum in a Child of Eight Years, *Am J Dis Child* 26 411-417 (Nov) 1923.

4 Bohrer, J. V., and Lincoln, E. M. Ganglioneuroma of the Chest in Children. A Report of a Case with a Review of the Literature, *J Thoracic Surg* 3 365-373 (April) 1934.

5 Bigler, J. A., and Hoyne, A. Ganglioneuroma. Report of Two Cases with a Review of the Literature, *Am J Dis Child* 43 1552-1571 (June) 1932.

* Division of Surgical Pathology, Mayo Clinic.

Dr. Gray (from the Division of Surgery, Mayo Clinic) and Dr. Shepard (who was a Fellow in Surgery, Mayo Foundation) are now, respectively, Captain and Lieutenant (ig), Medical Corps, United States Naval Reserve. The work reported in this paper was done before they entered the service.

1 Wohl, H. R. Neuroblastomata, with a Study of a Case Illustrating the Three Types That Arise from the Sympathetic System, *I M Research* 30 205-260 (May) 1914.

2 Wohl, H. R. and Craig, P. E. Multiple Tumors of the Sympathetic Nervous System. Report of a Case Showing a Distinct Ganglioneuroma, a Neuroblastoma and a Cystic Calcifying Ganglioneuroblastoma, *Am J Pathol* 14 797-807 (Nov.) 1938.

cyanosis. Some of the commonest symptoms, and often the earliest ones, are those due to pressure on the inferior laryngeal nerves—a change in the quality of the voice, a brassy cough and, much later, stridor. Encroachment on the bronchi may produce cough and the physical signs of decreased aeration. A generalized sensation of tightness or fulness in the thorax is often described by the patient harboring a growing mediastinal tumor. Dysphagia is rare, probably owing to the ease with which the esophagus accommodates itself to pressure. Edema of the upper half of the body, facial cyanosis and dilatation of the superficial veins may result from partial occlusion of the superior vena cava by pressure from a mediastinal ganglioneuroma. Involvement of the superior cervical ganglion causes enophthalmos, ptosis, miosis and lack of sweating (Horner's syndrome) on the homolateral side and is often seen in cases of ganglioneuroma of the superior mediastinum. Bizarre symptoms referable to the spinal cord may be due to pressure from a dumbbell-shaped tumor, which has grown into the spinal canal through an intervertebral foramen. Hart and Ellison⁶ observed the Pel-Ebstein type of fever among children who had a ganglioneuroma of the mediastinum. Cervical tumors are seen in conjunction with mediastinal ganglioneuroma at times, and these cervical masses are usually nerve tumors arising from the cervical portion of the sympathetic nervous system.

ROENTGENOLOGIC FINDINGS

Roentgenographically, the tumor appears as a dense homogeneous ovoid shadow arising in the posterior part of the thorax. The lateral border of the shadow is convex and sharply defined while the medial border adjacent to the vertebral column is definitely flattened. The lateral view shows that the mass arises in the posterior gutter of the thorax (the site of the sympathetic chain). No invasion of contiguous structures is seen, although the adjacent ribs or vertebrae may show thinning or erosion, owing to pressure from the tumor. Rarely, the tumor may grow through an intervertebral foramen and enlarge the foramen. Dolley and Jones⁷ recommended artificially induced pneumothorax to show that the tumor is extrapulmonary.

DIAGNOSIS

The typical picture is a mediastinal tumor which may be silent and found only accidentally.

⁶ Hart, F. D., and Ellison, P. O. Mediastinal Ganglio-Neuroblastoma, abstracted, *Proc Roy Soc Med* 30: 1195-1198 (Aug.) 1937.

⁷ Dolley, F. S., and Jones, J. C. Surgical Treatment. Tumors of Lung and Mediastinum. *Am Rev Tuberc* 39: 479-487 (April) 1939.

or by compression may cause a variety of symptoms, the most common being brassy cough, dyspnea and stridor. The patient's good general condition, the lack of signs of metastasis and the extremely slow growth of the tumor all point to a ganglioneuroma.

Differential Diagnosis—Driving goiter must be ruled out. This usually can be done by examining the patient's neck while he is swallowing. Mediastinal cysts may simulate ganglioneuroma in all respects, but only rarely are they encountered in the posterior gutter, whereas ganglioneuroma always arises posterior to the plane of the trachea. Dermoid cysts in the mediastinum are almost universally encountered in the anterior mediastinum. Mediastinal lymphoblastoma, especially Hodgkin's disease, may simulate ganglioneuroma. High voltage roentgen therapy serves to distinguish the two conditions, as irradiation has no effect on ganglioneuroma. Neurofibroma is supposedly distinguished from ganglioneuroma by the erosion of ribs and of the intervertebral foramina in the former condition, however, the same changes are encountered in ganglioneuroma.

TREATMENT

The only satisfactory treatment is surgical removal of the tumor. Irradiation with roentgen rays and radium is useless.

Bohrer and Lincoln recommend the establishment of an artificial pneumothorax two weeks before operation for the purpose of showing the presence of pleural adhesions, stabilizing the mediastinum and shunting the blood to the contralateral lung.

Complete excision is desirable, although some authors state that leaving part of the capsule of the tumor does not affect the prognosis. Excision is often made difficult by the presence of large blood vessels running over or through the tumor. At times, the tumor is firmly adherent to adjacent ribs or vertebrae and can be removed only by excision of the involved bony structures.

The entire thoracic sympathetic chain should be examined as ganglioneuromas are often multiple and even an examination of the entire thoracic chain does not exclude their presence in the abdomen or pelvis.

The posterior approach is the better one as the tumor originates in the posterior mediastinum and the great vessels lie between an anterior approach and the tumor.

An intercostal incision usually suffices although one or more ribs may have to be resected if the tumor is large especially if the ribs are firmly adherent to the growth. Some surgeons close the thorax without drainage while others insert a soft rubber catheter.

It is often extremely difficult or impossible to mobilize or remove a mediastinal ganglioneuroma because of its dense attachment to contiguous ribs or the bodies of the vertebrae. In addition, undue force cannot be exerted in their separation because of the danger of injuring important adjacent blood vessels and nerves.

COMPLICATIONS

Hemorrhage at times complicates the removal of mediastinal ganglioneuromas owing to their proximity to the large vessels of the posterior mediastinum.

As in any intrathoracic operation infection is to be feared but rarely complicates operations on these tumors as they are extrapleural.

Eloesser⁸ reported the removal of a mediastinal ganglioneuroma and the connected nerve, a meningopleural fistula and meningitis developed, but the patient recovered.

Various types of complications referable to the spinal cord may occur if a dumbbell-shaped tumor lies partly within the spinal column.

Riggs and Good⁹ reported a case in which fatal suffocation was due to tracheal obstruction by a contiguous ganglioneuroma.

Recurrence of these tumors is denied by James and Curtis¹⁰ and by Bohrer and Lincoln, however, many authors believe that they tend to recur, especially if they are incompletely removed. Malignant changes occur and metastasis has been encountered by Sophian¹¹ and by Clarke¹².

PATHOLOGY

Grossly, ganglioneuroma resembles uterine fibromyoma in color and consistency. It is usually encapsulated, although Sophian said that the capsule is often incomplete. Occasionally, it is lobulated, certain tumors are dumbbell shaped. Multiple tumors are sometimes seen, and often a single nerve or plexus of nerves is attached to one or more of the tumors. Hart described an outer yellow white cortex and an inner medulla showing regions of hemorrhage and necrosis.

8 Eloesser, L. Meningopleural Fistula Following Extirpation of a Ganglioneuroma of the Upper Mediastinum. *Ganglioneuroma of the Adrenal Gland*, S. Clin. North America **13** 1325-1336 (Dec.) 1933.

9 Riggs, T. F., and Good, L. P. Ganglioneuroma of Mediastinum Requiring Surgical Intervention for Relief of Obstructive Symptoms, *Arch. Surg.* **19** 309-320 (Aug.) 1929.

10 James, A. G., and Curtis, G. M. Mediastinal Ganglioneuroma. *Ann. Surg.* **113** 767-776 (May) 1941.

11 Sophian, L. Mediastinal Ganglioneuroma, *Ann. Surg.* **101** 827-833 (March) 1935.

12 Clarke, J. M. Large Thoracic Ganglio-Neuroma. *Austral. & New Zealand J. Surg.* **8** 199-202 (Oct.) 1938.

Microscopically, the tumor is mainly composed of fusiform cells arranged compactly, the nuclei are oval or round, are small and stain deeply with hematoxylin and eosin. Scattered throughout are islands of ganglion cells with little supporting fibrous tissue, but frequently surrounded by numbers of so-called satellite cells. The nerve fibers are mostly nonmedullated and often arranged in bundles. A greater number of axis cylinders than ganglion cells is often observed and is said to be due to degeneration of previously existing ganglion cells. The ganglion cells may be mononuclear or multinuclear, and Nissl granules can be demonstrated within the cytoplasm, as often seen in the normal state. Pigmentary degeneration or calcification of the ganglion cells is seen not infrequently. The tumor matrix is almost avascular white fibrous connective tissue.

Crile and Ball,¹³ Haven and Weil,¹⁴ Clarke and others described changes in the tumor which varied from the presence of primitive neuroblasts to adult ganglion cells. Such a tumor is probably best called ganglioneuroblastoma, as described by Hart, such a designation has the advantage of denoting the malignant potentialities of the tumor in contradistinction to the "benign" ganglioneuroma.

REPORT OF CASES

We report 3 cases of mediastinal ganglioneuroma that were observed at the Mayo Clinic one year.

CASE 1—The patient was a 9 year old boy whose family and past history were unimportant. Six months before the patient came to the clinic his appetite had become poor and two months before his admission at the clinic he had had an attack of influenza. Roentgenograms of the thorax at that time had disclosed a thoracic tumor. During the week before his admission to the clinic he had had shooting pains in the left side of the thorax.

The results of physical examination were normal except for dulness to percussion and decreased breath sounds at the base of the right side of the thorax posteriorly and laterally. The value for the hemoglobin was 112 Gm per hundred cubic centimeters of blood. The results of other tests, including Kahn's test, determination of the sedimentation rate and a tuberculin test were normal.

Anteroposterior and lateral roentgenograms of the thorax disclosed a mass in the lower posterior part of the right side of the thorax. There apparently was some pressure erosion of the inferior border of the tenth rib near the costovertebral juncture (fig. 1).

The diagnosis was ganglioneuroma of the right side of the thorax.

13 Crile, G. W., and Ball, R. P. Primary Malignant Tumors of Neck and Mediastinum, *Surg., Gynec. & Obst.* **48** 449-460 (April) 1929.

14 Haven, H., and Weil, A. Multiple Ganglioneuromas, *Arch. Path.* **13** 713-715 (May) 1932.



Fig 1—Roentgenographic appearance of ganglioneuroma in case 1, *a*, anteroposterior view showing discrete tumor in the lower medial part of the right half of the thorax, *b*, lateral view showing tumor arising in the posterior mediastinum

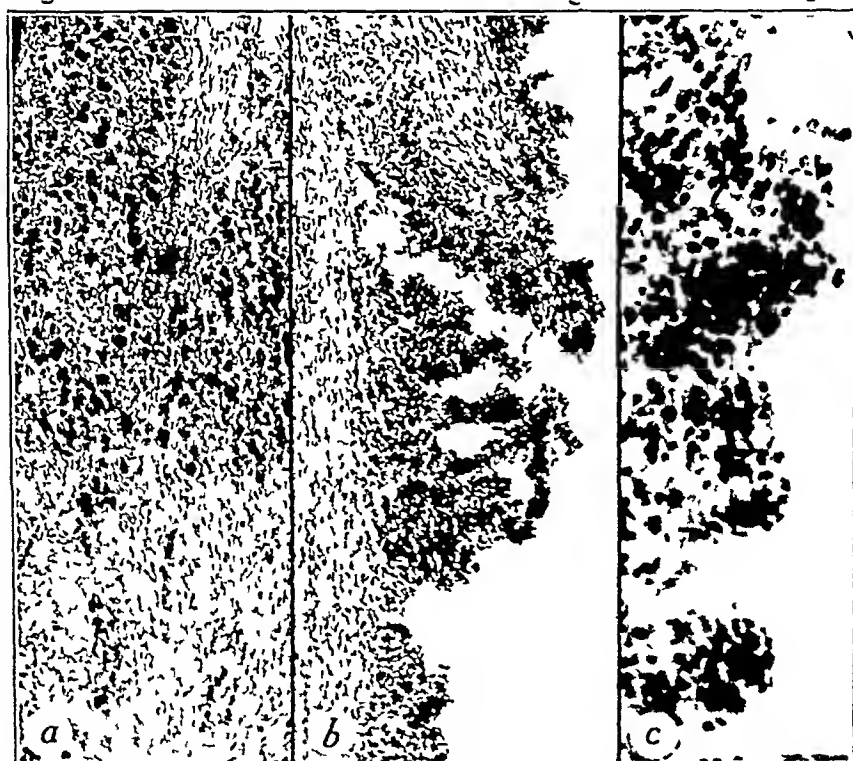


Fig 2—Photomicrographs of ganglioneuroma in case 1 sections stained with hematoxylin and eosin. *a*, numerous ganglion cells surrounded by amylinated nerve fibers, no malignant cells are visible ($\times 45$) *b*, portions show primitive (malignant) neuroblasts ($\times 45$) *c*, primitive neuroblasts ($\times 200$)

Operation—The right pleural space was opened by a curved incision in the ninth intercostal space on the right side. A smooth tumor 6 by 4 by 3 cm was seen in the right posterior gutter, it was densely attached to the right lateral aspect of the bodies of the vertebrae. The tumor was dissected free with difficulty. The wound was closed without drainage. Convalescence was uneventful.

Pathologic Aspects—Grossly, the tumor consisted of a lobulated dense tough fibrous mass measuring 6 by 4 by 3 cm. Its color varied from white to yellow. The appearance was quite similar to that of a uterine fibroma which had undergone fatty degeneration.

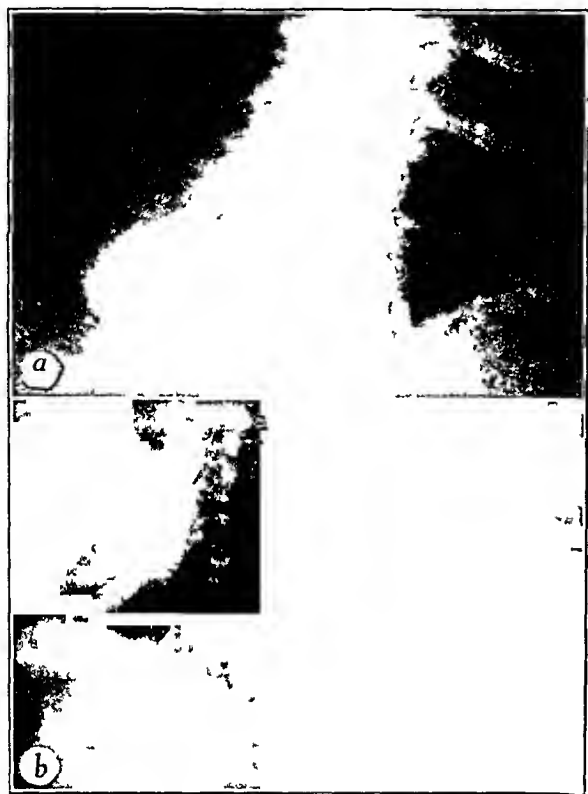


Fig 3—Roentgenographic appearance of ganglioneuroma in case 2, *a*, anteroposterior view showing large circumscribed tumor in lower medial part of the right half of thorax, the sharply defined shadow is rather characteristic of that produced by a ganglioneuroma, *b*, oblique view showing tumor in the posterior mediastinum.

Microscopically there was an avascular stroma of white fibrous connective tissue through which coursed numerous unmyelinated nerve fibers. There also appeared numerous elongated cells with large oval dark-staining nuclei. Large ganglion cells were numerous. They contained clear light-staining cytoplasm with large round nuclei containing nucleoli. Numerous primitive forms of nerve cells (neuroblasts and thus potentially malignant cells) were seen (fig 2).

Comment on Case 1—In this case the tumor like many mentioned in the literature was silent and found only when attention was drawn to it by roentgenographic examination of the thorax. It is said that the younger the patient the greater the likelihood that the tumor contains more primi-

tive (malignant) cells. The finding of such cells in this tumor supported this contention.

CASE 2—The patient was a married woman 35 years of age. She had sustained an injury to her back 4 years before she came to the clinic, this had not confined her to bed but she had had minor backache at irregular intervals since the injury. Two months before she came to the clinic she had undergone cholecystectomy and appendectomy, since the operation she had had a constant aching in the midline of the lower part of the back. The pain had extended into the shoulders and had been aggravated by standing or sitting. She came to the clinic because of this backache.

The results of physical examination were negative except for dullness to percussion and absence of sounds over a triangular area in the posterior part of the right side of the thorax.

The results of laboratory examinations, including urinalysis, an erythrocyte count, a leukocyte count, estimation of the value for the hemoglobin, a Kahn test and determination of the sedimentation rate, were normal in all respects. Roentgenograms of the thorax revealed a sharply defined soft tissue mass in the posterior part of the right side of the thorax at the costophrenic angle (fig 3). The upper margin of the tumor



Fig 4—Photomicrograph of ganglioneuroma in case 2, scattered ganglion cells are surrounded by bundles of unmyelinated neurons. No malignant nerve cells visible. Section stained with hematoxylin and eosin (×45).

extended to the body of the twelfth thoracic vertebra, the lower portion was not visible. The tumor was intrathoracic and contiguous to the spinal column. It did not interfere with diaphragmatic excursion. It appeared to be some erosion of the lower anterior corner of the body of the ninth thoracic vertebra at its external surface. Roentgenoscopic examination did not reveal

any pulsation of the tumor. The preoperative diagnosis was neurofibroma.

Operation—The right pleural space was opened through an incision in the right tenth interspace. This revealed a soft tumor, 10 by 15 cm, in the right retropleural region along the borders of the ninth thoracic to the eleventh thoracic vertebrae. The tumor was densely adherent to the thoracic wall and bodies of the vertebrae and could not be dissected free. A specimen was removed for biopsy, and the wound was closed without drainage.



Fig 5—Roentgenogram of ganglioneuroma in case 3

Pathologic Aspects—The microscopic structure of the tumor was the same as that of the tumor in case 1, except that the ganglion cells were much less numerous (fig 4). No neuroblastic elements were encountered.

Comment on Case 2—It is doubtful that the tumor had any relation to the backache as the patient was much improved when seen three months after operation. This tumor represents the type described in the literature as being impossible of removal owing to the dense adherence to bony structures.

CASE 3—The patient was a single man 26 years of age. His past history was unimportant. On routine roentgenographic examination of the thorax conducted at an army camp, a thoracic tumor was discovered.

Physical examination disclosed only dulness to percussion over the posterior superior portion of the left half of the thorax. The results of laboratory examinations including urinalysis, estimation of the value for the hemoglobin, an erythrocyte count, a leukocyte count, a K_{lin} test and determination of the sedimentation rate, were normal. Roentgenograms of the thorax revealed a well circumscribed tumor in the left superior part of the left half of the thorax. The tumor had caused erosion of the vertebral portions of the fourth and fifth ribs and separation of these ribs with widening of the intercostal space. The roentgenologic diagnosis was a neurofibroma arising from the fourth thoracic trunk or fourth intercostal nerve on the left (fig 5). Roent-

genographic examination of the thoracic and cervical vertebrae did not reveal any evidence of intraspinal extension of the tumor. The preoperative diagnosis was intrathoracic neurofibroma.

Operation—A curved incision was made along the vertebral border of the left scapula. The scapula was retracted medially, and most of the left fifth rib was removed from the angle anteriorly. The tumor measured 14 by 8 by 7 cm and was densely adherent to the left lateral aspect of the second to the sixth thoracic vertebrae and corresponding ribs in the posterior gutter. The tumor was so densely adherent to the fourth rib on the left side that the posterior 7 cm of the rib was removed with the tumor. The wound was closed without drainage. Convalescence was uneventful.

Pathologic Aspects—The gross appearance of the tumor was quite similar to that in case 1. Sections of various portions of the tumor were practically identical with the sections obtained in case 1 but ganglion cells were much less frequent. No malignant cells were seen (fig 6).



Fig 6—Photomicrographs of ganglioneuroma in case 3, sections stained with hematoxylin and eosin, a, characteristic ganglion cells arranged in groups and surrounded by myelinated nerve bundles ($\times 45$), b, section containing two large ganglion cells whose cytoplasm is filled with Nissl bodies, the small dark cells are the periganglionic 'satellites' ($\times 435$).

Comment on Case 3—As is commonly the case the tumor was discovered quite by accident and had caused no symptoms. Its removal was difficult owing to its dense adherence to the bony structures of the thoracic cage.

PROGRESSIVE EXOPHTHALMOS IN TOXIC DISEASE OF THE THYROID GLAND

A REVIEW OF THE RECENT LITERATURE, WITH THE REPORT OF A CASE OF PROGRESSIVE POST-THYROIDECTOMY PROPTOSIS IN A SIX YEAR OLD NEGRO GIRL

MAJOR GEORGE M. HAIK

MEDICAL CORPS ARMY OF THE UNITED STATES

Exophthalmos has been recognized as a phase of the syndrome of hyperthyroidism literally since the recognition of the disease, as the nomenclature of exophthalmic goiter shows. Persistent or progressive post-thyroidectomy exophthalmos has been recognized as a possible undesirable and a potentially serious sequel of the operation almost from the time the surgical treatment of hyperthyroidism was introduced. The successful therapy of postoperative exophthalmos, however, is little more than a decade old, and intensive study of the problem of both preoperative and postoperative proptosis has been carried out for an even shorter time, so short a time in fact, that Means's¹ statement in 1942 that "a new specialty of endocrinologic ophthalmology is a-borning" seems unduly optimistic.

CAUSATION OF EXOPHTHALMOS ASSOCIATED WITH HYPERTHYROIDISM

Statements concerning the clinical aspects of exophthalmos are widely divergent. Paulson² and Cattell³ could find no correlation between the severity of the hyperthyroidism and the degree of exophthalmos, though Cattell demonstrated a definite correlation between its degree and the duration of the thyroid disease. Plummer and Wilder⁴ stated that in large groups of patients the severity of the proptosis can be correlated with the severity of the hyperthyroidism, as shown by high basal metabolic rates and weakness of the quadriceps femoris muscles.

From the 64th General Hospital, and from Charity Hospital of Louisiana at New Orleans

1 Means, I. H. Diseases of the Thyroid Gland. New England J. Med. **227**: 594-602 (Oct. 15) 1942.

2 Paulson, D. L. Experimental Exophthalmos and Muscle Degeneration Induced by Thyrotropic Hormone. Proc. Staff Meet., Mayo Clin. **14**: 828-832 (Dec. 27) 1939.

3 Cattell, R. B. Eye Complications in Exophthalmic Goiter, Cataracts and Exophthalmos. Ann. Surg. **100**: 284-293 (Aug.) 1934.

4 Plummer, W. A., and Wilder, R. M. Etiology of Exophthalmos: Constitutional Factors with Particular Reference to Exophthalmic Goiter. Arch. Ophthalm. **13**: 822-852 (May) 1935.

There is now fairly general agreement that exophthalmos is likely to be most severe after operation in subjects whose preoperative exophthalmos has been of long duration, and it is also agreed that it does not occur either before or after operation in the absence of toxicity.

There is no agreement as to the incidence of post-thyroidectomy exophthalmos, chiefly because, as several recent writers have pointed out, few statements are based on accurate measurements if on any measurements at all. Plummer and Wilder found it difficult to understand why a few patients should present exophthalmos after operation while the majority lose such degrees as they presented before thyroidectomy and show no signs of its recurrence. Cattell in a statistical study, stated that almost 75 per cent of the patients followed up had complete or partial relief from their preoperative exophthalmos. Lehman⁵ considered postoperative improvement due rather to disappearance of spasm of the levator muscles and narrowing of the palpebral fissures than to recession of the eyes. He also cited Ruedemann's observations, based on careful measurements, to the effect that the average postoperative recession amounts to only 2 mm.

The studies of Soley⁶ and of Galli-Maimini⁷ in 1942 support Lehman's observations. Soley, who emphasized that the loss of stare associated with hyperthyroidism does not necessarily mean a decrease in exophthalmos, showed by exophthalmometric measurements that the eyes of over 50 per cent of patients with diffuse toxic goiter become measurably more prominent after subtotal thyroidectomy, and also showed that recession occurs in only a small percentage of cases.

5 Lehman, J. A. Hyperthyroidism in Children. West J. Surg. **44**: 528-534 (Sept.) 1936.

6 Soley, M. H. Exophthalmos in Patients with Various Types of Goiter. Arch. Int. Med. **70**: 206-220 (Aug.) 1942.

7 Galli-Maimini, C. Exophthalmometric Measurements in Patients with Thyroid Diseases with Some Discussion of Their Significance. Ann. Int. Med. **16**: 415-426 (March) 1942.

Galli-Mainini concluded, also on the basis of exophthalmometric measurements, that while patients with no history of exophthalmos during the course of their illness present normal measurements after thyroidectomy, those with recognized protrusion during the active phase of their illness always have some postoperative persistence of the exophthalmos

The various theories advanced to explain exophthalmos include (1) sympathetic overactivity, (2) relaxation of the extraocular musculature, (3) contraction of smooth muscle in the floor of the orbit, (4) vascular abnormalities, including dilatation of the orbital vessels with congestion of the vascular bed of the orbit, and retrobulbar venous engorgement, (5) increase in the orbital fat, (6) edema of the normal orbital contents, which may or may not be associated with edema of the extraorbital structures, and hypertrophy of the extraocular muscles (so-called hypertrophic myositis)

Most of these theories receive little credence at this time although certain cases are observed in which even the most unlikely does not seem inapplicable. Cattell,⁸ for instance, pointed out that the apprehensive or actually frightened expression of a subject with hyperthyroidism suggests a sympathetic influence, while the rapidity with which gross exophthalmos often disappears after correction of hyperthyroidism suggests a nervous origin rather than anatomic intraorbital change. Actually, however, the theory of sympathetic overactivity has little to support it.

The theory of increased vascularity suggested by Trousseau⁸ in 1865 and by Filehne⁹ in 1879 was based on the experimental observation that enucleation of normal eyes was not attended by the profuse hemorrhage which occurred when similar operations were performed on exophthalmic rabbits. Daily and his associates¹⁰ have recently reported a case in which the same phenomenon was observed, venous congestion was so marked while decompression was being done that constant suction was necessary to keep the operative field clear. Eagleton,¹¹ after a detailed discussion of the anatomy and blood supply of the orbit, reasoned that a physiologic increase in the

amount of blood within the retrobulbar space is promptly compensated for as long as the veins and arteries possess their normal contractile properties, but that retention of arteriovenous blood within the limited intraorbital space necessarily results in exophthalmos. The theory is not universally applicable and does not explain the case to be reported herewith.

The most commonly accepted explanation of exophthalmos is the theory of local structural edema, which may be associated with muscular hypertrophy. These theories do not necessarily conflict with the theory of increase in the orbital fat. As several recent writers have pointed out, older reports are based on gross inspection and not on histologic examination, which, had it been carried out, might have revealed precisely the same changes reported by more modern writers. Another prolific source of confusion is the fact that muscle sections are notoriously difficult to interpret.

Edema of the orbital tissues in exophthalmos was first mentioned by Jones¹² in 1860, and in the last several years it has been repeatedly described in the still sparse histologic studies made in such cases. The first really comprehensive investigations were made by Naffziger,¹³ who removed 20 specimens of muscle in the course of ten decompression operations. In every instance, apparently from a combination of edema and hypertrophy, the structures were from three to ten times larger than normal. The muscles frequently felt hard and were sometimes rubbery hard and fibrotic. In the most advanced cases the tissue was gritty to the knife. Histologic changes included in varying degree swelling of the muscle fibers, loss in striations, definite interstitial edema, lymphocytic infiltration and scar tissue. Naffziger's examinations were unusually complete, and permitted the statement that early, intermediate and late stages of pathologic change may all be found in the same tissue. Failure to confirm his observations by some writers may perhaps be due to less complete examinations. Whatever the reason, discrepancies have been reported. Thomas and Woods¹⁴ found hypertrophy of the muscle in only 1 of 3 recent cases and slight enlargement and degeneration in only 1 of 6 restudied specimens. On

⁸ Trousseau, cited by Swift²³

⁹ Filehne, cited by Swift²³

¹⁰ Daily, R. K., Daily, L., Walker, J. D., and Peterson, H. J. Exophthalmic Ophthalmoplegia, *South M. J.* **35** 344-352 (April) 1942

¹¹ Eagleton, W. P. Exophthalmos from Surgical Diseases, Especially as to Involvement of the Protective Retrobulbar Space, *Arch. Ophth.* **14** 1-40 (July) 1935

¹² Jones, cited by Means¹

¹³ Naffziger, H. C. Progressive Exophthalmos After Thyroidectomy, *West J. Surg.* **40** 530-543 (Oct) 1932

¹⁴ Thomas, H. M., and Woods, A. C. Progressive Exophthalmos Following Thyroidectomy, *Bull. Johns Hopkins Hosp.* **59** 99-113 (Aug.) 1936

the other hand, Ellett¹⁵ found muscular hypertrophy in both of his cases, Daily and his associates¹⁰ found it in 2 of 3 cases. Klemme¹⁶ found it in 1 of 2 cases, and Semmes,¹⁷ in a single case, found the muscles ten times normal size. While muscular hypertrophy is thus not universal, edema is generally observed. It was the only obvious explanation of the exophthalmos in the case reported herewith, in which degenerative changes were also observed.

Experimental exophthalmos comparable to human exophthalmos has been extremely difficult to produce, and only the use of pituitary extract has been in any way successful. Since recent studies supply considerable support of the theory of edema with or without associated muscular hypertrophy, one or two may be briefly mentioned. Smelser¹⁸ for instance, by injections of beef pituitary extract, was able to produce definite and sometimes extreme exophthalmos in from twelve to twenty days in 47 of 50 thyroidectomized young adult guinea pigs. The exophthalmos varied in degree but was roughly proportionate to the amount of pituitary extract used. It did not disappear post mortem but often became more pronounced as the lids relaxed, particularly in the group of animals in which cervical sympathetic ganglionectomy had also been done. The histologic changes in the experimental animals were identical with those in 2 clinical cases observed by Smelser, in both of which the eyes were lost because of corneal damage. Except for degenerative changes they were also similar to the observations reported by Naffziger. Smelser concluded that the changes which he observed were secondary and were caused by mechanical or toxic factors inherent in lowered tissue nutrition.

Aird¹⁹ produced experimental exophthalmos in guinea pigs by intraperitoneal injections of various extracts of anterior pituitary gland containing the thyrotropic fraction. It progressed slowly and irregularly, but persisted after the

injections had been discontinued as well as during narcosis and after death. Myopathy of the extraocular muscles was sufficient to account for both the degree and the permanence of the proptosis, and it was Aird's opinion that it was qualitatively consistent with changes found in the extraocular muscles of human subjects with malignant exophthalmos.

Paulson² observed protrusion of the eyeballs within twenty-four hours after the first injection of an anterior pituitary extract which contained potent quantities of thyrotropic factor (antuitrin T) in 80 per cent of intact animals and in all thyroidectomized animals. The mean percentage of water in the retrobulbar tissues of treated animals, exclusive of the lacrimal glands, was 6.37 per cent greater than in the tissues of intact animals, although the percentage in the lacrimal glands and in the skeletal and cardiac muscles of treated animals was not significantly greater than in similar tissues of untreated control animals.

MODERN CONCEPTS OF EXOPHTHALMOS ASSOCIATED WITH HYPERTHYROIDISM

Both experimental and pathologic evidence thus points to edema of the orbital structures, with or without muscular hypertrophy, as a reasonable explanation of exophthalmos. Even after this fact has been established, however, several problems still remain to be solved. One is the fundamental cause of the edema. Here the recent studies of Means and his associates²⁰ and the speculations based on them throw considerable light. These authors, who conceive of exophthalmic goiter as a state of "total endocrine imbalance," call attention to the fact that the thyroid and its hormone and the anterior pituitary gland and its thyrotropic (thyroid-stimulating) hormone are apparently concerned with water balance as well as with metabolism. The thyroid hormone has been shown to promote diuresis and the thyroid-stimulating hormone of the pituitary to promote storage of water. Since the hormonal balance can be altered in more than one way, these authors do not find it unreasonable that in certain cases of exophthalmic goiter the nature of the imbalance is such that storage of water is the chief manifestation or that the consequences of such storage in the orbit because of limitations of space, may be disastrous.

The most difficult problem of all is why exophthalmos progresses after thyroidectomy in a cer-

15 Ellett, E. C. Unilateral Exophthalmos. *J. A. M. A.* **116** 1-7 (Jan. 4) 1941.

16 Klemme, in discussion on Scott, G. W. Malignant Exophthalmos and Operative Approach, *West. J. Surg.* **43** 119-126 (March) 1935.

17 Semmes, in discussion on Naffziger, H. C., and Jones, C. W. The Surgical Treatment of Progressive Exophthalmos Following Thyroidectomy. *J. A. M. A.* **99** 638-642 (Aug. 20) 1932.

18 Smelser, G. K. A Comparative Study of Experimental and Clinical Exophthalmos. *Am. J. Ophthalm.* **20** 1189-1203 (Dec.) 1937.

19 Aird, R. L. Experimental Exophthalmos and Associated Myopathy Induced by the Thyrotropic Hormone. *Ann. Int. Med.* **15** 564-581 (Dec.) 1941.

20 Means, J. H., Hertz, S., and Williams, R. H. Graves' Disease with Dissociation of Thyrotoxicosis and Ophthalmopathy. *Tr. A. Am. Physicians* **56** 67-74 1941.

tain small proportion of cases, since in the majority, even if it does not completely regress it at least becomes stationary or shows no gross increase. The once accepted idea that it is progressive because sufficient thyroid tissue has not been removed is scarcely tenable in view of the fact that removal of additional tissue often not only does not correct the condition but may, as in the reported case, be followed by further aggravation of the proptosis.

Thomas and Woods¹⁴ have correctly emphasized that hypothyroidism is scarcely a reasonable explanation since exophthalmos is never observed after total thyroidectomy for heart disease. Seitchik's²¹ suggestion that post-thyroidectomy exophthalmos is caused by an increased secretion of thyrotropic hormone in subjects in a hypothyroid state is purely theoretic.

The observations of Means and his associates,²⁰ however, seem to throw considerable light on postoperative exophthalmos. In addition to their concept of hyperthyroid disease as a state of "total endocrine imbalance," they have made two classifications of the disease. In one, the classic variety, thyrotoxicosis is the major problem. In the other, which they have named "Graves' disease with dissociation of thyrotoxicosis and ophthalmopathy" and which they call the "special ophthalmic type" as a matter of convenience ophthalmologic considerations are predominant. Indeed, as in the case reported herewith the patient frequently first seeks medical attention on account of his eyes. There are also other differences between this type and the classic type.

1 Thyrotoxicosis is mild, absent, or readily controlled. This criterion does not fit the reported case, in which toxicity was severe and was extremely difficult to control.

2 Enlargement of the gland is not notable.

3 Males are affected relatively more often than females though exophthalmic goiter is more frequent in females than in males.

4 Response to iodine is superstandard, the basal metabolic rates often reaching minus levels. This occurred in the reported case, in which however, the levels were never unusually high in view of the child's extreme toxicity.

5 The ocular signs differ somewhat from those of the classic type in which the conspicuous features are exophthalmos, lid lag and lid retraction. In the special ophthalmic type of case exophthalmos is relatively slight but there

may be marked periorcular edema, chemosis of the conjunctiva sometimes accompanied by massive swelling, injection of the conjunctiva and smarting and excessive watering. Ophthalmoplegia and diplopia are also frequent. Most of these signs were present in the reported case in which however the classic ocular signs were also present and in which exophthalmos was marked.

THERAPY

The methods of attacking exophthalmos collected by Naftziger¹³ in 1932 included such palliative procedures as tarsorrhaphy and canthotomy, incision of the lid and plastic operations on the conjunctiva, and such radical procedures as removal of the periorbital fat and the Kionlein operation. Cervical sympathetic ganglionectomy has been advocated, but the results are so poor that the operation has been generally discarded, and Hernandez Ramirez and Hernandez's²² report of a successful case is distinctly out of the ordinary.

The operation which Naftziger¹³ devised in 1932 after one of his patients with progressive exophthalmos had committed suicide has given generally good results in the limited number of cases in which it has been employed. It is, however, a serious procedure, as is shown by the fatal outcome in the reported case, in which it was done by an experienced neurosurgeon. Swift's²³ method of decompression through a lateral approach is also a serious procedure.

Sewall,²⁴ in studying the Naftziger technique, realized that an equal or even greater amount of space about the orbit might be gained by utilizing the neighboring sinuses. He therefore devised an operation which consists of incision through the skin of the orbit, entrance into the frontal and ethmoid sinuses, complete removal of the orbital walls, evertion of the ethmoid cells and resection of the floor of the orbit. Kistner²⁵ employed this operation in 2 of his 3 cases and considers that it has several advantages over the Naftziger operation. Dalk and his associates¹⁶

22 Hernandez Ramirez, R, and Hernandez A. A. Residual Exophthalmos After Thyroidectomy in Basedow's Disease. Cervical Sympathectomy, Arch de Otol de Buenos Aires **15** 58-64 (Feb.) 1940 abstracted Am J Ophth **25** 369 (March) 1942.

23 Swift, G. W. Malignant Exophthalmos. Tr. Am. A. Study Goiter 1935 pp. 1-10.

24 Sewall, E. C. Operative Control of Progressive Exophthalmos. Arch. Otolaryng. **24** 621-624 (Nov.) 1936.

25 Kistner F. B. Decompression for Exophthalmos. Report of Three Cases. I. A. M. A. **112** 37-38 (Jan. 7) 1939.

21 Seitchik, I. N. Mechanism of the Production of Exophthalmos in Exophthalmic Goiter. Arch. Ophth. **27** 762-775 (April) 1942.

however, have pointed out that if the frontal sinuses are small the Naffziger operation promises better results

The obvious defect of even the best of these operations is that it is directed toward correcting a condition which has already developed and is not concerned with its prevention. Such preventive measures as are available are not entirely satisfactory. Bandaging, the use of cotton pledgets and of supersaturated petrolatum gauze, and lubrication of the eyes during anesthesia are appropriate measures in all cases but are merely palliative. Opinions differ as to the value of cellophane shields, which Ruedemann²⁷ recommends. He has pointed out the illogic of suture of the lids, edema cannot be corrected by this method and pressure will only be magnified against the cornea or the sutures. He has sometimes found it useful to bring up the lower lid by Frost's method using a collodion dressing to help support the skin of the face.

If the views of Means and his associates²⁸ are accepted, the idea that increasing exophthalmos is an indication for immediate thyroidectomy is no longer tenable. The poor results which frequently follow operation seem to support their opinion that thyroidectomy is the measure most definitely contraindicated in this variety of hyperthyroidism and feeding of thyroid the method most definitely indicated. The basis of the latter suggestion is then personal experimental studies which show that thyroidectomy promotes retention of water, while feeding of thyroid promotes diuresis.

Means and his group have outlined a plan of therapy for patients with the "special ophthalmic type" of hyperthyroidism, which includes the use of both iodine and thyroid extract, the former for its effect on the basal metabolic rate and the latter for its diuretic effect. If thyrotoxicosis is so extreme that it must be treated, irradiation is preferred to thyroidectomy, which should be a last resort, on the ground that it has a more gradual effect on the hormonal balance and therefore permits a more gradual readjustment of the optic structures. Means and his associates also used irradiation of the pituitary gland in 1 case with good results, the rationale of the method being their concept of the role of the thyroid-stimulating hormone in the "special ophthalmic type" of goiter. If edema of the orbit is of sudden onset or if it is extreme, diuretics may be useful as a temporary measure or repeated lumbar puncture may be carried out.

Soley,⁹ whose work was presented at about the same time as that of Means and his associates, in general shares these views. His concept is that the only reasonable explanation for progressive exophthalmos after thyroidectomy is the rapid change from a state of hyperactive function of the thyroid to a normal or subnormal state. He also advocates the substitution of irradiation for thyroidectomy as a more gradual method of bringing about this change.

Feeding of thyroid for progressive exophthalmos after thyroidectomy has been tried with varying results. Thomas and Woods¹¹ used this method in 5 of their 15 cases with no effect at all, and the results at the Mayo Clinic, where it has been used in combination with iodine therapy since 1922, do not seem to be striking.²⁸ On the other hand, Willard Bartlett Jr.²⁹ has reported success with it in 2 cases, in 1 of which there was almost complete loss of vision. In the other, intense edema about the orbit was part of a general myxedema. The results might perhaps be better if Bartlett's warning were generally heeded that feeding of thyroid be instituted without delay when an increase in exophthalmos is observed after thyroidectomy. It seems scarcely necessary to emphasize that if this method is used either before or after operation, there should be frequent determinations of the basal metabolic rate.

REPORT OF A CASE

These studies, most of which are recent, seem to throw light on a case of exophthalmic goiter with progressive post-thyroidectomy proptosis observed a number of years ago in a young Negro child at the Charity Hospital of Louisiana at New Orleans. Had they been available at the time, the outcome of the case might possibly have been different.

History.—A D, a Negro girl aged 6, was brought to Charity Hospital of Louisiana at New Orleans Sept. 23, 1936 because "her eyes were coming out of her head." Until nine months before she had been a healthy child. Then her parents first observed bilateral protrusion of the eyes, it had progressed gradually until two weeks before her admission to the hospital after which progress had been rapid. Three months before admission it was observed that she had become extremely nervous and was constantly covered with

27 Means J H. The Eye Problems in Grave Disease. *Illinois M J* 80:135-138 (Aug) 1941.

28 Haines in discussion on Paulson.

29 Bartlett in discussion on Naffziger H C, and Jones, C W. The Surgical Treatment of Progressive Exophthalmos Following Thyroidectomy. *J A M A* 99:635-642 (Aug 20) 1932.

26 Ruedemann A D. Exophthalmos. *Bilateral Exophthalmos in Adults*. *Cleveland Clin Quart* 3:281-291 (Oct) 1936.

perspiration. She had lost a great deal of weight in these three months, although her appetite had become progressively larger. The only subjective complaint was palpitation.

Examination—Physical examination showed a well developed child, who had apparently lost considerable weight. She was quiet and unusually intelligent for her age and race, but seemed apprehensive. The temperature was 99.6 F, the pulse rate 136 and the respiratory rate 32 per minute and the blood pressure 110 systolic and 40 diastolic. There was visible pulsation of the vessels of the neck, and the heart was slightly enlarged, a soft systolic murmur was heard in the aortic, pulmonary and tricuspid areas.

The expression was fixed and staring and bilateral exophthalmos (graded plus 4) was present. The pupils were equal and regular and reacted to light and in accommodation. The palpebral fissures were greatly widened. Ocular signs included lid lag, inability to converge and failure of the forehead to wrinkle when the patient looked up. Visual acuity was within normal range.

Urinalysis, serologic tests of the blood and spinal fluid and roentgenologic examination of the skull revealed no abnormalities. Examination of the blood showed 4,650,000 red cells and 12,350 white cells per cubic millimeter. The hemoglobin was 90 per cent. Roentgenologic examination of the chest revealed an enlargement of the cardiac shadow in the transverse diameter. The initial basal metabolic rate was plus 26.

Treatment and Preoperative Course—Treatment consisted of complete rest in bed, a high caloric diet, fluids by mouth pushed to the limit of toleration and fluids given parenterally as necessary to maintain the proper fluid balance. Administration of strong solution of iodine U S P in doses of 5 minims (0.3 cc) three times daily was begun on September 30.

For a few days there was considerable improvement, though the pulse rate was never less than 120 per minute. Then nervous symptoms and restlessness became increasingly marked, there were daily elevations of temperature to 102.5 F, the pulse rate rose to 168 per minute, diarrhea was profuse, and by October 5 the child was in clearcut crisis. Administration of iodine was discontinued and routine measures for the control of crisis were instituted. Transient improvement was followed by a second crisis, but after October 20 improvement was continuous, though the pulse rate was seldom lower than 120 to 140 per minute.

Medication with strong solution of iodine had been resumed in 5 minim doses three times a day on October 11. After October 20 it was given in 10 minim (0.6 cc) doses three times a day in cycles of four days of medication and one day of rest. After November 25 it was discontinued entirely. The basal metabolic rate, originally plus 26, was minus 4 on October 8, minus 32 on October 22 and plus 24 on November 23. Examination of the blood on October 25 showed 4,960,000 red cells and 9,250 white cells per cubic millimeter. The hemoglobin was 100 per cent. The cholesterol content of the blood on October 29 was 170 mg per hundred cubic centimeters.

Management of the exophthalmos, which had increased steadily since the child's admission to the hospital, had meantime become a serious problem. On October 15 marked bilateral conjunctivitis and episcleritis were observed. A fold of edematous conjunctiva protruded from the lower portion of each eyeball overhanging the lower lid and preventing closure of the eyes. The left eye showed a beginning ulceration of the cornea with some infiltration of the lower third probably from ex-

posure and 'strangulation.' There was a moderate bilateral purulent discharge. Conservative measures including hot compresses, boric acid ointment and taping of the lids produced so much improvement that tarsorrhaphy which had been advised on October 24, was postponed.

First Operation—The left lobe of the thyroid, which was now stony hard, probably as the result of long-continued therapy with iodine, was removed on December 3. The immediate postoperative course was stormy but after the fourth day improvement was continuous and the patient was dismissed from the hospital on Dec 27, 1936. At this time the basal metabolic rate was plus 27. The condition of the right eye was fairly satisfactory but the left eye showed an opacity at the site of the corneal infiltration.

Serial tests of the function of the liver by the Quick hippuric acid test had been carried out and were interpreted as indicative of grave and possibly permanent damage to the liver. The highest value, 67 per cent of normal, was obtained immediately after the child's admission to the hospital. During the periods of crisis the values fell to 50 and later to 25 per cent of normal. After lobectomy the value was less than 20 per cent of

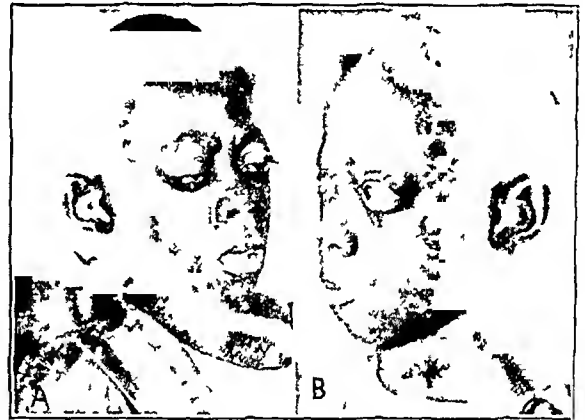


Fig 1—A, progressive bilateral exophthalmos eleven months after lobectomy. B, progressive exophthalmos of left eye two months after excision of right eye and thirty-five days after second stage thyroidectomy.

normal, and when she was dismissed it had risen to only 30 per cent of normal.

Second Admission—The child was brought back to the hospital on Nov 1, 1937, eleven months after the first operation. She had gained some weight and was in generally better health. The temperature was 99 F, the pulse rate 100 and the respiratory rate 24 per minute and the blood pressure 130 systolic and 88 diastolic. The thyroid gland was moderately enlarged, especially on the right side.

The eyes had not shared in the general improvement but had become progressively more protuberant. A week before the child's return the right eye had become reddened and painful, and a day or two later some discharge was noted. Examination showed a marked bilateral exophthalmos (fig 1 A). The conjunctiva of the right eye was greatly reddened there was a grayish exudate over the cornea and a moderately profuse yellowish discharge was present, a smear from which revealed numerous pus cells but no bacteria. A diagnosis of panophthalmitis was made and excision was stated to be inevitable but because of improvement under conservative therapy it was postponed until November 12.

Second Operation—On November 12 the right eye was eviscerated. By this time the left eye was slightly injected. It was treated with continuous boric acid compresses and boric acid ointment three times a day

and less than 20 per cent of normal on two succeeding occasions, which confirmed the original impression of grave and probably permanent damage to the liver. Administration of strong solution of iodine was begun



FIG. 2—A, section of orbital muscles removed at Naftziger decompression operation. Note the lymphocytic infiltration, the swelling and edema of the muscle fibers and the absence of cross striations. B, section of orbital muscles removed at autopsy nine days after Naftziger decompression operation. Note the absence of lymphocytic infiltration and the less marked edema of the muscle fibers. Cross striations, although indistinct, are now present.

and later by insufflations of atropine sulfate ointment and daily bandaging.

The result of a Quick hippuric acid test of function was 73 per cent of normal on the initial test

in 10 minute doses three times a day on November 29 and by December 8 the basal metabolic reading was 60.

Third Operation—On December 9 lobectomy was performed on the right side with the patient under solution

of tribromethanol-ether anesthesia Recovery was fairly smooth, the maximum pulse rate being 154 per minute Postoperative therapy included a transfusion of 250 cc of whole blood

The child's general condition showed considerable improvement after operation, though her appetite continued insatiable and there was no corresponding gain in weight The pulse rate varied between 100 and 120 per minute She was permitted to be up most of the time and played about the ward with the other children

In the meantime, however, the condition of the remaining eye continued to deteriorate (fig 1B) Intraocular pressure was normal, and the fundi and pupillary reflexes were also normal, but the orbital tissues showed extreme tension and edema Exophthalmos progressed to such a degree that the lids no longer covered the eyeballs, corneal ulceration was also progressive, and keratitis developed

Fourth Operation—On Jan 11, 1938, when it was clear that no results could be expected from conservative therapy and that only radical measures might save the remaining eye, the Naffziger unroofing operation, preceded by tarsorrhaphy, was carried out under local anesthesia with solution of tribromoethanol The operation was without incident except for a slight tearing of the dura The orbital fat and ocular muscles were markedly edematous and a section of the superior rectus muscle (fig 2A) was reported on as follows "The muscle fibers are somewhat edematous and pale Cross striations are not observed A small amount of hemorrhage is present A slight lymphocytic infiltration is observed"

The postoperative course was uneventful for twenty-four hours On the second day the temperature rose to 104 F and the pulse rate to 160 per minute On the third day a spinal tap revealed bloody cerebrospinal fluid under pressure of 14 mm of mercury On the fifth day infection of the scalp wound was evident, the sutures were removed and the wound was opened widely Symptoms of meningitis became progressively clear-cut, and death occurred from this cause on the ninth postoperative day

Autopsy—Postmortem examination revealed acute leptomeningitis, abscess of the left frontal lobe of the brain, extreme fatty metamorphosis of the liver and cloudy swelling of the convoluted tubules of the kidney The optic structures (fig 2B) were reported on as follows "The optic nerve and the coats of the eyeball show no abnormalities The extraocular muscles are pale and slightly edematous Their cross striations are invisible The nuclei are large and vesicular"

COMMENT

Aside from its ophthalmologic aspects, this case is of interest for other reasons Toxic thyroid disease in very young children is unusual, and in very young Negro children it is even more unusual In Boyce's³⁰ study of thyroid disease at the New Orleans Charity Hospital over a recent twelve and a half year period there were 183 cases of toxic goiter in Negroes, only 2 of which, including the reported case, occurred

30 Boyce, F F Thyroid Disease in the Southern Negro A Comparative Analysis of 470 White and 482 Negro Cases from Charity Hospital of Louisiana at New Orleans, Surg, Gynec & Obst 70 761-767 (April) 1940

in children under 15 years of age The other child, incidentally, a girl 8 years old, died on the operating table A casual search of the literature has revealed no other instance of progressive post-thyroidectomy exophthalmos in a young colored subject

Of the devastating character of this patient's toxicity there can be no doubt It was evidenced by her extreme nervousness, her voracious appetite with continued loss of weight or lack of gain of weight, her constantly elevated pulse rate, respiratory rate and temperature, the crises which developed on two occasions, and the degree of damage to the liver demonstrated ante mortem by serial tests of function and confirmed by postmortem examination The case, unfortunately, was handled at a most unpropitious time, when the new Charity Hospital was in course of construction During this period the makeshift buildings in which the population was housed were hopelessly overcrowded, especially those for Negroes, and the special nursing, isolation and quiet, which are among the cardinal principles of the management of hyperthyroidism, were impossible of achievement The child had to be kept in an open ward, in most of the beds of which there were at least 2 patients Boyce³⁰ and Maes and Romano³¹ have called attention to the difficulties attending the treatment of hyperthyroidism during this period, and Boyce has reported 4 cases of adults in which the noise and confusion incident to the hospital construction seemed to play a definite part in the fatal outcome

It should also be pointed out that the child's parents disregarded the instructions given them when she was dismissed after the first operation, and ten months (instead of three) had elapsed and irreparable damage to the eyes had occurred before she was brought back for further treatment

The optic tissues removed at operation showed edematous changes, which were also present, though to a lesser degree, in the tissues removed at postmortem examination (fig 2) The case thus seems, in most respects to fit into the "special ophthalmic type" of goiter described by Means and his associates²⁰ It may be that the use of irradiation rather than thyroidectomy, as advocated by these authors and by Solev,⁶ might have saved the child's eyes and ultimately her life, though this comment of course is not intended as a criticism of the treatment employed which met all the criteria for the therapy of

31 Maes L and Romano S A Thyroid Disease in a Nonendemic Area A Third Series of Observations Ann Surg 111 275-284 (Feb) 1940

exophthalmic goiter as it was then conceived. On the other hand, the child's toxicity was of such a degree that it presented a threat to life and was in the beginning an even more serious problem than her progressive exophthalmos. Whether the outcome of the case might have been different had the child's parents brought her back at the appointed time, so that the second lobectomy could have been performed promptly is another matter for speculation.

SUMMARY AND CONCLUSIONS

The treatment of exophthalmos associated with hyperthyroidism, particularly of the variety which becomes progressive after thyroidectomy, has hitherto been unsatisfactory.

Thyroidectomy, far from correcting the condition, frequently seems to aggravate it.

Recent studies indicate that the cause of exophthalmos in hyperthyroidism is local edema, sometimes associated with hypertrophy of the extraocular muscles.

The proposal that irradiation be substituted for thyroidectomy is based on the theory that with a less abrupt alteration in the endocrine balance there is a greater chance for more gradual readjustment of the optic structures.

A case of progressive post-thyroidectomy exophthalmos is reported and is analyzed in the light of these new concepts. It is unusual because of the extreme youth and the race (Negro) of the patient.

LATERAL ABERRANT THYROID METASTASIS TO THE LYMPH NODES FROM PRIMARY CARCINOMA OF THE THYROID GLAND

RICHARD C CLAY, MD,* AND SAM S BLACKMAN JR, MD
BALTIMORE

For over fifty years cystic papillary growths of thyroid tissue in the lateral cervical region have been recognized, but the interpretation placed on them has almost uniformly been that they represent embryonically misplaced thyroid tissue. This explanation is implicit in the term in Shrager's¹ generally accepted nomenclature, "lateral aberrant thyroid." Recently it has been shown clearly by King and Pemberton² that these "lateral aberrant thyroid" masses are in reality metastases from a carcinoma of similar structure in the thyroid gland itself.

The following 2 cases recently seen at the Johns Hopkins Hospital confirm the work of King and Pemberton. While 2 cases constitute a small series, they are reported as additional evidence that papillary cystic thyroid tissue in the lateral cervical region is often metastatic from an identical primary tumor in the thyroid. Since the primary tumor may be extremely small, exploration of the thyroid and removal of at least the homolateral lobe are indicated.

REPORT OF CASES

CASE 1—A white man 21 years old first came under observation in October 1941. He had always been well. In the course of a routine physical examination a mass 3 cm in diameter was palpated deep in the right supraclavicular region. When removed two weeks later it was found to lie beneath the sternocleidomastoid muscle.

The specimen was a brownish, cystic, gelatinous, encapsulated mass measuring 2 by 2 by 3 cm and was thought to be lateral aberrant thyroid tissue. Microscopic examination revealed a papillary cystadenocarcinoma of thyroid tissue in a lymph node together with less differentiated masses of epithelial cells invading the capsule and the remaining lymphoid follicles and sinuses (fig 1). The final diagnosis was "carcinoma invading cervical lymph node and capsule of papillary cystadenoma of aberrant thyroid."

The patient remained well and repeated roentgenograms showed that his chest was normal. He was followed in the outpatient department. In May 1943,

eighteen months after the first operation, in the course of another routine physical examination, a firm mass was felt in the right supraclavicular region. An exploration of the neck was performed a few days later and two masses, each 1.5 cm in diameter, were found. One lay beneath the internal jugular vein and the second inferiorly and posteriorly in the posterior mediastinum. The right lobe of the thyroid was exposed and found by palpation to contain two small nodules in the posterior part. This lobe was accordingly removed. The opposite lobe was normal to palpation and was left in place.

Examination of the specimens revealed that in the right lobe of the thyroid there was a tumor 1 cm in diameter, and loosely attached to the lower margin of the lobe was another 5 mm in diameter. These nodules proved to be identical with the lesion removed from beneath the sternocleidomastoid muscle nineteen months before (fig 2). The cervical nodules were clearly metastases in lymph nodes from the tumor in the thyroid. Remnants of the lymph nodes could be seen at the margins of the metastases. The primary lesion in the thyroid and all the metastases contained cystic papillary areas, acinus-forming areas with colloid, and foci of solid undifferentiated tumor cells. There were also small scattered foci of calcification in all the lesions.

The patient has been treated with irradiation since his discharge, remains well, and shows no recurrence six months after operation. His lungs remain clear and no calcified foci can be seen in the neck or mediastinum on roentgen examination.

CASE 2—A white woman, aged 26, was first seen in 1937 complaining of a swelling in the left side of her neck. It had been present for four years and was growing larger. Her health had been excellent and the past family histories were noncontributory. Physical examination revealed three masses at the posterior border of the left sternocleidomastoid muscle said to be comparable in size to a lemon, a hen's egg and a walnut respectively. Biopsy of one of these masses showed what was thought to be a papillary tumor of thyroid tissue, probably arising in aberrant thyroid tissue (fig 3A). Accordingly all the masses, which were found to be encapsulated, were subsequently excised. The thyroid was exposed and was thought by the operator to be normal. Microscopically the excised masses were identical with the tissue in the biopsy specimen, and the final diagnosis was papillary cystadenoma of aberrant thyroid.

In connection with the study of case 1 in June 1943, the microscopic sections from case 2 were reviewed. In all of them a good deal of lymphoid tissue was found, mostly about the periphery of the nodules. In some sections the lymphoid tissue contained germinal centers and lymph sinuses, which clearly indicated that it was not simply lymphoid follicles which are sometimes found in papillary tumors of the thyroid, but the residue of lymph nodes containing metastases from the

* Harvey Cushing Fellow in Surgery.

From the Surgical Pathology Laboratory of the Departments of Pathology and Surgery of the Johns Hopkins University.

1 Shrager, V. L. *Lateral Aberrant Thyroids*. Surg, Gynec & Obst 3: 465, 1906.

2 King, W. L. M., and Pemberton, I. de I. *So-Called Lateral Aberrant Thyroid Tumors*. Surg, Gynec & Obst 74: 991, 1942.

tumor in the thyroid gland. A letter to the patient elicited the information that a slowly growing lump had been noticed in her neck for one year. For this reason she was requested to return and was admitted to the hospital in October 1943, six years after her first operation.

Physical examination on this occasion revealed a firm nodular mass, 4.5 by 3 cm, at the lower pole of the left lobe of the thyroid gland, but no palpable lateral cervical masses were felt. At operation the nodule was found in the lower pole of the left lobe,

of the thyroid and that in the lateral cervical region, there were two small nodules, 1 and 3 mm in diameter, in the right lobe of the gland. Microscopic sections showed that the large tumor was a papillary cystadenocarcinoma (fig 3B), while the extrathyroid mass was a metastasis in a lymph node, as evidenced by germinal centers and lymph sinuses in the surrounding lymphoid tissue (fig 3C). These structures were histologically identical with the metastases removed six years previously. The nodules in the right lobe were also small foci of papillary cystadenocarcinoma.

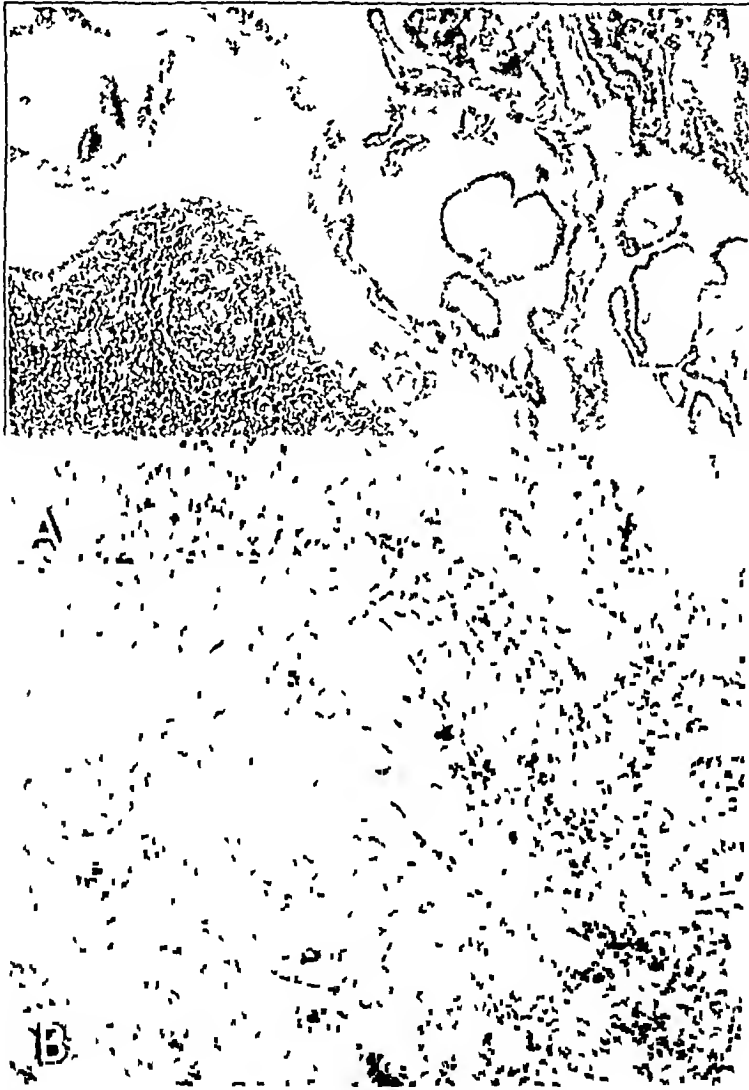


Fig 1—A, first metastasis of papillary cystadenocarcinoma removed from lateral cervical region in case eighteen months before the primary tumor in the thyroid was suspected. Remnants of the largely destroyed lymph node in which the metastasis lies can be seen here. B, another area from the section seen in A, showing undifferentiated tumor and small foci of calcification in the lymph node.

and a subtotal bilateral thyroidectomy was done. Further exploration of the neck and superior mediastinum revealed a single, encapsulated, soft, brownish nodule 2 cm in diameter, lying posterior to the lower pole of the left lobe between the esophagus and the carotid vessels, but completely detached from the thyroid gland. The nodule was removed, and no other masses were found.

Examination of the specimens showed that, in addition to the mass disclosed at operation in the left lobe

In this case, then, the primary carcinoma was palpable in the exposed thyroid at the time of removal of the first metastases, and only five years later it was noticeable to the patient. Meanwhile a metastasis developed which was apparently not present at first operation, was not felt on physical examination at the time of the second, and was discovered only at surgical exploration of the neck.

The patient's lungs and mediastinum show no evidence of metastases on roentgen examination at

time of writing, of course, with such slowly growing tumors this fact is of limited significance. She is to receive irradiation of the cervical region.

COMMENT

The suggestion that carcinoma in so-called lateral aberrant thyroids might actually represent metastasis from a primary tumor in the thyroid originated with Wohl.³ He reported a case of a 19 year old woman who had five lateral cervical

roid tissue in the lateral aspect of the neck might not be primary in lateral aberrant thyroid but metastatic from the thyroid itself.

Eberts⁴ was even more specific. Having seen 2 patients with "lateral aberrant thyroid tissue" who subsequently had "massive malignant disease in the homolateral lobe" of the thyroid when he again encountered a malignant papillary adenoma of "aberrant thyroid" associated with

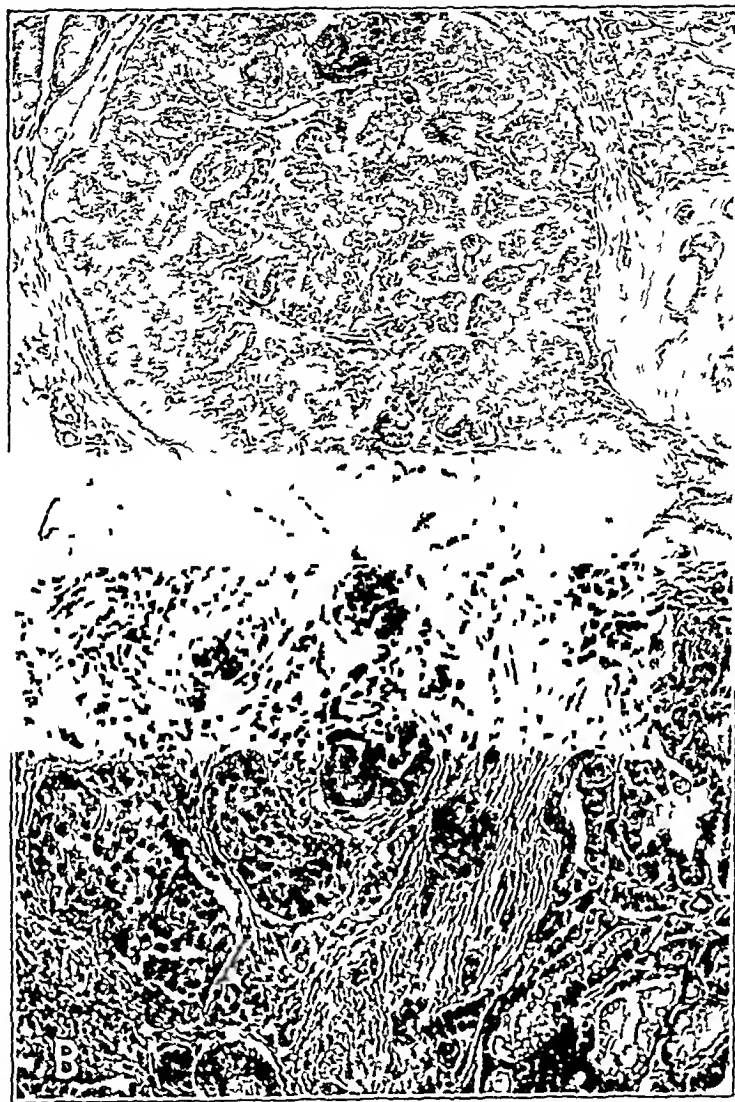


Fig 2—1, a focus of papillary cystadenocarcinoma from the right lobe of the thyroid in case 1. On purely histologic grounds this focus would be thought benign. B, an area of undifferentiated carcinoma from the right lobe of the thyroid in case 1.

nodules of which two showed "papillary adenocarcinoma" while the other three revealed metastases of the same tumor in lymph nodes. The patient had a very adherent indurated and slightly enlarged thyroid gland probably "carcinomatous," but biopsy was not performed. This author concluded that "carcinomatous thy-

roid tissue in the lateral aspect of the neck might not be primary in lateral aberrant thyroid but metastatic from the thyroid itself. Having seen 2 patients with "lateral aberrant thyroid tissue" who subsequently had "massive malignant disease in the homolateral lobe" of the thyroid when he again encountered a malignant papillary adenoma of "aberrant thyroid" associated with

³ Wohl M G. Carcinoma of Lateral Aberrant Thyroid. *Interstate M J* 24: 1044 1917.

⁴ Eberts E M. Lateral Cervical Aberrant Thyroid. *Canad M A J* 29: 32 1933.



Fig 3—*A*, lateral cervical lymph node metastasis from papillary cystadenocarcinoma of the thyroid gland in case 2 removed six years prior to thyroidectomy. At the time of removal of this specimen, no primary tumor was suspected. Remnants of the lymph node can be seen in the section. *B*, primary papillary cystadenocarcinoma from the left lobe of the thyroid in case 2. This tumor is identical with the previously removed metastasis seen in *A*. *C*, lymph node metastasis from papillary cystadenocarcinoma of the left lobe of the thyroid seen in *B*. This specimen lay detached from the thyroid, posterior to the lower pole, between the esophagus and the carotid vessels.

tion of lymph flow was away from the thyroid and toward the cervical nodes and that, as with certain other carcinomas, metastatic lesions sometimes outgrew the primary one. He concluded that "palpation, if negative, should be followed by exploration of the lobe."

Subsequently Pemberton⁵ stated in the course of general discussions on carcinoma of the thyroid that he believed papillary adenocarcinoma of so-called lateral aberrant thyroids was primary in the thyroid itself.

Frantz, Forsythe, Hanford and Rogers⁶ analyzed 30 cases of "lateral aberrant thyroid," interpreting 23 as malignant on histologic grounds. One of their alleged benign lesions, however, was stated to be in a lymph node, and, as our case 2 indicated, histologic criteria of benignancy of these lateral thyroid tumors is unreliable. Of these 23 patients, 16 had primary carcinoma in the thyroid gland, 1 had an "adenoma" not further described, and in 6 the thyroid was not removed because it seemed normal to the surgeon. In 7 cases some of the lateral cervical nodules removed were recognized as being metastases in lymph nodes from carcinoma of the thyroid. The data point inescapably to the fact that these tumors were primary in the thyroid, while the lateral masses represented metastases to the lymph nodes, although this point was not made by the authors. Among the 23 patients with malignant lateral cervical masses, 5 were known to have distant metastases, 1 having died five months after operation, 2 others having survived for eight and nine years postoperatively and another having died of intercurrent disease sixteen months after operation, while the fifth, operated on three years before the paper was written, was alive at that time.

Touroff⁷ has recently reported the case of a patient who had multiple lateral cervical nodules, one of which was found by biopsy to be papillary thyroid tissue. The nodules were subsequently removed along with the homolateral thyroid lobe, which was seen at operation to be enlarged 50 per cent due to a small discrete tumor. This tumor and the lateral cervical nodules all contained papillary thyroid carcinoma, and several of the lateral masses were recognized as lymph nodes containing metastatic thyroid tumor. The cervical nodules which failed

to reveal lymph nodes around the tumor were interpreted as aberrant thyroid, but there is no indication that multiple sections were made to ascertain whether recognizable lymph node was present at other points in the nodules. This case was interpreted as representing coexisting identical carcinomas of the thyroid gland and aberrant thyroid tissue, with metastases in cervical lymph nodes. An alternative explanation is that the tumor of the thyroid gland was primary while the lateral masses were all metastases in cervical lymph nodes.

King and Pemberton² have recently made clear that the relation between the "lateral aberrant thyroid" and the thyroid gland is that of metastasis and primary carcinoma. They reported 51 cases of malignant "aberrant thyroid" lesions in the lateral cervical regions, of which 31 were associated with carcinoma of the homolateral thyroid lobe, established by microscopic examination, inoperability or death. No microscopic examination of the other 20 thyroid glands was made. In 19 instances specimens of the thyroid gland and the lateral cervical mass were obtained and were found to be identical. Ten of the patients died of carcinoma of the thyroid gland, though 1 lived nineteen years postoperatively and another lived nine and one-half years after pulmonary metastases were demonstrated.

These authors also report 15 cases in which the diagnosis was conceded to be papillary carcinoma of the thyroid with metastases to cervical lymph nodes to show that they differ from the first series only in "relative degree of prominence of the clinical history and findings of the 'aberrant' or thyroid tumor." Even among these cases the primary carcinoma of the thyroid was found only at operation in 4 instances, while in 3 others the surgeon removed what he thought was a normal thyroid lobe only to have the pathologist find in it a small papillary carcinoma identical with the metastases. In 60 per cent of the cases of this series the lateral metastases contained lymphoid tissue, the same proportion which contained such tissue in the first group of 51 cases. The authors conclude that "aberrant thyroid tumors are not adequately treated until the homolateral lobe of the thyroid has been removed, whether or not a gross tumor is evident at operation."

The microscopic appearance of these cystic papillary tumors is not a reliable index of their malignancy (ability to metastasize). In 1 of the cases described in this paper, neither the primary tumor nor any of the metastases showed microscopic evidence of anaplasia. The tissue was cystic and papillary in pattern; there were no

5 Pemberton, J. de J. Treatment of Carcinoma of the Thyroid Gland, *Ann Surg* 100:906, 1934, Malignant Lesions of the Thyroid Gland, *Surg, Gynec & Obst* 69:417, 1939.

6 Frantz, V. K., Forsythe, R., Hanford, J. M., and Rogers, W. M. Lateral Aberrant Thyroids, *Ann Surg* 115:161, 1942.

7 Touroff, A. S. W. Coexisting Carcinomata of Thyroid and Aberrant Thyroid with Regional Metastases, *Ann Surg* 113:73, 1941.

mitotic figures, and there was little or no variety in the shape, size or chromatin content of the nuclei. The tumors in this case resembled exactly those which are usually described as papillary cystadenoma of the thyroid gland.

In the other case the primary tumor in the thyroid and the cervical metastases contained cells arranged in a variety of patterns. There were cystic and papillary areas, foci whose cells formed large acini full of colloid and small solid strands and masses of undifferentiated cells without any definite architecture. The cells arranged in these three ways showed little or no evidence of anaplasia.

Some authors,⁸ recognizing the frequent coexistence of "lateral aberrant thyroid" carcinoma with carcinoma in the thyroid itself, have interpreted the lateral mass as the primary tumor and the thyroid lesion as metastatic. Aside from the fact that such a route of metastasis is counter to the direction of lymph flow, such an interpretation is tenable only if it can be incontrovertibly shown that the lateral lesion is not a metastasis in a lymph node. Since a growing metastasis from a tumor destroys the node in which it lies, random sections of such a lateral cervical mass might well fail to show the architecture of the residual lymph node. In the cases reported in the literature the presence of lymphoid tissue in the lateral cervical masses is frequently noted, but there is no report of a careful search by multiple sections for the remains of a lymph node in the other cases. Until evidence is adduced to show cases in which such careful study of the lateral lesions fails to reveal remnants of lymph nodes and also in which the excised thyroid gland on thorough search reveals no carcinoma, the interpretation of the lateral lesions as primary and any concomitantly occurring lesions in the thyroid gland as metastatic cannot be proved. Such evidence is lacking. On the other hand, the 2 cases presented here in each of which the lateral masses were in lymph nodes and a similar tumor was found in the thyroid, together with the fact that in every case of King and Pemberton in which the thyroid was removed a tumor histologically identical with those in the lateral masses was found in the gland itself, point to the explanation that the

tumor in the thyroid is primary and the lateral masses metastatic.

SUMMARY

Two examples of the condition which has repeatedly been described in the medical literature during the past forty years as "lateral aberrant cervical thyroid" have been studied. In both cases the lateral cervical masses were found to be metastases in lymph nodes, while the primary tumor in each case was found in the homolateral lobe of the thyroid gland.

In one case the primary tumor was palpable only at operation, nineteen months after removal of the first metastases in cervical lymph nodes. In the other case three cervical metastases were removed at a time when no tumor was recognized in the exposed thyroid at operation. Six years later, however, another cervical metastasis was found and the primary tumor in the homolateral lobe of the thyroid was then about 4 cm in diameter. In this case there were small foci of papillary cystadenocarcinoma in the opposite lobe of the thyroid as well.

CONCLUSIONS

Evidence from the literature and from 2 additional cases indicates that the lesions long known as lateral aberrant cervical thyroid should be interpreted, until satisfactory evidence to the contrary is adduced, as tumor metastases in cervical lymph nodes from small primary carcinomas in the homolateral lobe of the thyroid. When such a lesion is found in the lateral cervical region, the thyroid should be explored, and at least the homolateral lobe should be removed, whether the primary tumor is palpable or not. The tumor may be present in both lobes of the thyroid, and if only one lobe is removed the patient should be watched for the subsequent appearance of lesions in the opposite lobe.

The spread of metastases to lungs, bones and other sites may be relatively slow, and this particular tumor seems therefore to represent a type of carcinoma in which there is reason to believe that the disease may be cured by surgical removal of the primary lesion and first metastases.

The microscopic appearance of these lesions is not a good index of malignancy since metastases develop which look histologically "benign."

Johns Hopkins Hospital

⁸ Lahey, F. H., Hare, H. F., and Warren, S. Carcinoma of the Thyroid, *Ann Surg* 112:977, 1940.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1942

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN
ACADEMY OF ORTHOPAEDIC SURGEONS

(Concluded from page 184)

XIX. FRACTURES

A FRACTURES EXCEPTING FRACTURES OF THE NECK OF THE FEMUR

PREPARED BY H. EARLE CONWELL, M.D., HERMAN F. JOHNSON, M.D., DON H. O'DONOGHUE, M.D., WALTER G. STUCK, M.D., AND EUGENE M. REGEN, M.D.

Fractures of the Clavicle—Hodgson⁴⁸⁹ reports a method for treatment of certain fractures of the clavicle which do not respond to ordinary methods or for which ordinary methods are contraindicated. The usual figure-of-eight bandage is applied to hold the shoulders back. The patient is then placed in bed with the head of the bed elevated, and a muslin bandage is passed through the figure-of-eight bandage on the affected side and around the head of the bed. The weight of the body slipping toward the foot of the bed maintains constant traction of the shoulder upward and outward. Hodgson states that this will reduce practically any fracture of the clavicle. It is necessary to keep the patient in bed, on the back, with a small pillow between the shoulder blades, for three to five weeks, until union is secure.

[ED. NOTE—While this method will undoubtedly maintain reduction in the majority of instances, it entails the disadvantage of keeping the patient in bed in one position for several weeks. It would seem that this treatment should be reserved for selected cases or used only as a method of reducing the fracture and followed by a fixation dressing which will permit the patient to be ambulatory.]

Slaughter⁴⁹⁰ reports on 5 patients with pathologic fractures of the clavicle and 3 patients with pathologic fractures of the ribs. All were persons who had been treated with radiation for carcinoma of the breast. There was no evidence of metastasis. All the fractures occurred during normal activity of the patients. Only 3 of the 8 patients were aware of the fracture, the lesions of the others were discovered in a routine check-up examination. The author points out that bone may be profoundly affected in the clinical use of radiation. He attributes this to two factors: (1) Bone absorbs more energy from radiation per unit of volume than any other tissue, and (2) because of the high calcium content of bone greatly increased secondary radiation is produced. He believes that massive doses of radiation will cause more damage to bone than fractional irradiation with the same total dose, since bone makes almost complete recovery from light doses but with heavy doses may undergo necrosis. In this stage there is no repair and the bone becomes a sterile foreign body. He warns against placing radium or radon near bone when it is used in interstitial irradiation.

Fractures of the Humerus—For supracondylar fractures of the elbow in children with extreme generalized swelling of the region or in cases in which closed reduction has failed, Hart⁴⁹¹ believes that manipulative reduction and maintenance of acute flexion are contraindicated. He has used 4 to 6 pounds (1.8 to 2.7 Kg.) of skeletal traction with a Kirschner wire through the proximal end of the shaft of the ulna (not through the olecranon process). The line of traction is directed upward and forward in relation to the elbow. Countertraction is obtained by utilizing the weight of the patient's body and by attaching a weight of 1 to 3 pounds (0.5 to 1.5 Kg.) to a padded linen towel and placing the towel over the abducted arm. The entire arm projects beyond the edge of the bed. Elevation of the side of the bed or insertion of sand bags between the mattress and the springs protects the child

489 Hodgson, F. G. A Treatment for Fractured Clavicle by Traction, South M. J. 35 1079-1080 (Dec.) 1942.

490 Slaughter, D. P. Radiation Osteitis and Fractures Following Irradiation with Report of Five Cases of Fractured Clavicle, Am. J. Roentgenol. 48 201-212 (Aug.) 1942.

491 Hart, V. L. Reduction of Supracondylar Fractures in Children, Surgery 11 33-37 (Jan.) 1942.

from falling out of bed [ED NOTE (L D B) —Too careful watch cannot be maintained if countertraction is applied by a weight suspended over the abducted arm, as palsy of the radial nerve may develop in a surprisingly short time. In many cases the same force can be obtained by cutaneous traction to the forearm. Sides to the bed with the arm extending through the side can be used for countertraction provided the posts are well padded.]

Winfield, Miller and LaFerte⁴⁹² believe that the "hanging cast" method of treatment of fractures of the humerus is most effective. They point out that it does not depart from established principles as widely as is generally supposed, as it is one of the best examples of the use of traction. The muscles of the arm are relaxed when the arm is hanging at the side, so the deltoid muscle does not displace the fragments. They use a pad on the inner side of the cast at the bend of the elbow if a fracture of the middle or lower third of the humerus has a tendency to assume a varus position. Manipulation is used, as it has been found that the traction cast will produce excellent functional and satisfactory anatomic results. Care must be taken not to use too heavy a cast, since distraction may be produced particularly with transverse fractures. One hundred and three cases are reviewed. The average time the cast was worn was forty-seven and one-half days. In summary, this method is applicable to most fractures of the humerus, the cast is cheap, simple and easy to apply, it is comfortable, it permits ambulation of the patient and allows early mobilization of the joints, the period of hospitalization and the amount of physical therapy required are reduced to a minimum, the incidence of delayed union and of nonunion is low, and the end results are equal to or better than those obtained by other methods. [ED NOTE (L D B) —This detailed analysis of such a large number of cases helps to establish the use of the hanging cast as the standard treatment for fractures of the humerus.]

Breck and Basom⁴⁹³ employ a posterior molded plaster splint for simple fractures of the shaft of the humerus without displacement, after closed and open reductions and after bone graft operations. The splint extends from a point just lateral to the base of the neck, over the point of the shoulder and then posterolaterally over the upper part of the arm, elbow and forearm to the middle of the hand, leaving the fingers free. The arm hangs by the side with the elbow at a right angle and the wrist straight. A generous pad of sheet wadding is placed in the axilla and a small pad in the antecubital fold. The splint is held in place with gauze roller bandage, and when the plaster has set woven elastic bandages are applied over the gauze bandage. The arm is then placed in a sling, and another circular piece of muslin encircles the upper part of the arm and the body, pinning the arm to the body. A special harness-like piece of apparatus, made of duck with adjustable straps and buckles, is then applied. [ED NOTE (L D B) —Recent reports indicate that an attempt to produce fixation of the shoulder joint is not necessary in treating fractures of the humerus. It appears that the hanging cast with circumduction exercises for the shoulder is the treatment of choice.]

Stuck and Hinchey⁴⁹⁴ review 129 cases of fracture of the shaft of the humerus as regards the form of treatment and the end results. The hanging cast treatment (19 cases) gave the best results. Union was more rapid and no nonunion occurred. The other methods were abduction splints or casts (57 cases) delayed or nonunion in 9 cases, lateral traction in bed (23 cases) delayed or nonunion 1 case, open reduction was necessary in only 9 cases, or 7 per cent. [ED NOTE (L D B) —This is an excellent review.]

Fractures About the Elbow—MacAusland⁴⁹⁵ gives the advantages of use of a longitudinal screw or nail over that of absorbable suture in the treatment of fractures

492 Winfield, J. M., Miller, H., and LaFerte, A. D. Evaluation of "Hanging Cast" as Method of Treating Fractures of Humerus, *Am J Surg* 55:228-249 (Feb) 1942.

493 Breck, L. W., and Basom, W. C. A Modified Moulded Splint for Fractures of the Shaft of the Humerus, *South Surgeon* 11:410-413 (June) 1942.

494 Stuck, W. G., and Hinchey, J. J. Fractures of the Shaft of the Humerus, *South Surgeon* 11:305-315 (May) 1942.

495 MacAusland, W. R. The Treatment of Fractures of the Olecranon by Longitudinal Screw or Nail Fixation, *Ann Surg* 116:293-296 (Aug) 1942.

of the olecranon as (1) better reduction, (2) better retention (3) shorter disability and (4) motion in four to five days, against four to five weeks with the use of suture. He points out that effective treatment depends on two factors: accurate anatomic reposition of fragments and sufficient fixation. He uses a screw of sufficient length to engage the cortex of the distal fragment. Exercises of the fingers and shoulder are started on the second day to preserve the tonicity of the muscles. Gentle motion of the elbow in flexion and extension can usually be started on the fourth or fifth day. Removal of the screw or nail in six months is optional. [ED NOTE (L. D. B.)—The author has discussed one of the better methods of treating olecranon fractures. It should be remembered that frequently no definite choice can be made as to the method of treatment. If the proximal fragment is small excision does not interfere with function of the elbow and aids early recovery.]

Observation of over 1,000 cases of fracture about the elbow led Conwell⁴⁹⁶ to several conclusions. In manipulation of supracondylar fractures, if there is no displacement the elbow should be flexed and this position maintained. Flexion will be free when reduction is complete unless limited by swelling. The degree of flexion for immobilization of the forearm varies inversely with the swelling. It is extremely important to watch the circulation in any case of injury of the elbow. Traction should be applied to the forearm, keeping it in full extension with elevation to 45 degrees when much swelling is present. Aspiration of the hematoma, or even incision and drainage, may be necessary. Ischemic paralysis or even gangrene may result if too acute flexion is used. Skeletal traction is important in the treatment of compound fractures of the lower end of the humerus. The author advocates use of sulfanilamide as well as of sulfathiazole in treating these wounds.

A fracture of one of the condyles, if the fragment is displaced, usually requires open reduction. If the fragment is large in a fracture of the capitellum, it may be reduced by direct pressure while the forearm is adducted and slightly flexed. If reduction is impossible, arthrotomy is indicated for reduction or removal of the fragment. A fracture of the olecranon in which there is separation of the fragments requires open reduction and fixation by stainless steel wire. Motion should be started in seven to ten days.

Fractures of the head and neck of the radius are found to occur rather frequently since the increased use of roentgen rays, not only as isolated injuries but with other injuries of the elbow. Operative treatment is advocated if as much as one third of the head is broken off and displaced. Displacement interferes with free motion of the elbow. If the fragment is small the surgeon is justified in waiting to see how much limitation of motion results before operating.

Dislocations of the elbow are next in frequency to those of the shoulder, posterior displacement being more common. A definite click is felt in reducing these, after which there is little or no resistance in flexion. One should immobilize in as much flexion as is safe according to the swelling present. Flexion should be maintained by a posterior plaster splint for ten to fourteen days with gradual extension thereafter.

Lee⁴⁹⁷ contends that the serviceable elbows which result after fracture of the humeral condyles in children are due to the reparative power of the children rather than to good treatment of the fractures. An analysis of 32 cases is presented, with a report of the end results. Some of the patients were seen twenty-two years after the injury. Although equally good results were seen to have been produced by open and by closed methods there was marked difference in the end result roentgenograms. Malunion and overgrowth of the condyles were evident in the patients treated by a closed method, while those treated operatively showed accurately replaced and well developed condyles. Slight limitation of motion in the elbow may be disregarded by both the patient and the physician as the joint bears no

⁴⁹⁶ Conwell H. E. Fractures About Elbow Joint Especially in Children, *Nebraska M. J.* 27:229-232 (Jul.) 1942.

⁴⁹⁷ Lee H. G. Fractures of the Humeral Condyles in Children, *Surg. Gynec. & Obst.* 75:97-102 (Jul.) 1942.

weight and its useful range is 60 degrees of flexion to 130 degrees of extension. The author suggests chromic catgut or a vitallium nail for fixation of the fragment in open reduction. Solid healing should be allowed before motion is started. Forcing the joint causes further damage. Motion will return with use provided there is no bony block or formation of scar tissue.

Neuwirth⁴⁹⁸ has treated a series of fractures of the elbow joint by the non-splinting method, because so many poor functional results have occurred with splinting and because small fragments near a joint are difficult to control by external splinting even when accurate reduction has been accomplished. The arms of the patients treated without splinting were placed in triangular bandages suspended from the neck, with the elbows flexed. Movement of the elbow joint as well as of the arm was encouraged as soon as pain had subsided. A group of 5 cases is presented, in which all the patients regained 100 per cent function. Neuwirth contends that the nonsplinting method of treatment should be the rule and fixation and splinting the exception.

After a review of the literature and of the end results in 16 cases of fracture of the head of the radius in children, Roosvall⁴⁹⁹ draws the following conclusions: 1. Fractures without or with only moderate displacement (to an angle of 45 degrees) should be treated conservatively. 2. Reduction by manipulation can be used also for severe fractures, yielding good ultimate results. 3. In cases of greater displacement of fragments, in which reduction by manipulation has failed, early operative reduction is to be preferred to extirpation of the displaced fragments. 4. In the case of extirpation, synostosis between the radius and the ulna occurs to a great extent, and sometimes also reduction of flexion and extension in the elbow. 5. In the cases in which the fragment has been removed one also gets a fairly pronounced valgus formation in the elbow as a result of removal of the epiphysis with consequent impaired growth. A tabular analysis of the 16 cases is presented. Open reduction was done in 3 cases. In 4 cases extirpation was done owing to the marked displacement of the upper fragment. Nine patients were treated conservatively. Of these, 5 were free from subjective symptoms. In 8 the configuration of the elbow was normal, and in 6 function was normal. Good results were obtained in all except 1 case, in which rotation was impossible owing to bony synostosis between the radius and the ulna. Of the 3 patients treated by open reduction who were followed up, all were free from subjective symptoms. In 1 case there was normal mobility. [ED. NOTE (L. D. B.)—This report is a warning against too early and too radical operation for fractures of the head of the radius.]

Cohn⁵⁰⁰ reviews fractures of the elbow and points out the dangers of loss of motion unless reduction is accomplished. In the diagnosis, careful clinical examination should be performed. Roentgen examination alone can give a false sense of security, especially in cases of fractures in children. It is essential to know the date of appearance, the relationship of and the age of complete ossification of the epiphyses in children if roentgenograms are to be interpreted properly. The capitellum is the only epiphysis which is apparent prior to the fifth year. A common source of confusion is the appearance of the epiphysis for the olecranon. It sometimes ossifies through two separate centers, but more often through a single center, with ossification proceeding from the tip down. Not uncommonly one will find a report of a fracture which does not exist. Excess callus formation developing later in untreated patients may impair motion of the joint.

Operation about the elbow involving the epiphyses should be avoided if possible in children. If a fracture of the internal epicondyle epiphysis cannot be completely reduced, removal of this epiphysis does not cause disturbance of function of the elbow. Every effort should be made to avoid the development of Volkmann's ischemia. When it develops, fasciotomy is indicated, but exposure of the arteries

498 Neuwirth, A. A. Nonsplinting Treatment of Fractures of Elbow Joint, *J. A. M. A.* 118:971-972 (March 21) 1942.

499 Roosvall, A. Fractures of Neck of Radius in Children, *Acta chir. Scandinav.* 85:540-556, 1941.

500 Cohn, I. Fractures of Elbow, *Am. J. Surg.* 55:210-227 (Feb.) 1942.

is not recommended. Fractures of the head of the radius with displacement usually require resection, and the author describes a method of operative exposure. Operation is indicated in many cases of fractures of the upper third of the ulna, to avoid angulation of the proximal fragment and the resultant partial ankylosis.

For severe comminuted supracondylar fractures in which multiple fragments are present, skeletal traction by means of a Kirschner wire in the upper portion of the ulna just below the olecranon is the best method. If there are not too many fragments and reduction is not accomplished, an operation employing the approach through a trap door in the triceps tendon advocated by Van Gorder with the use of screws and plates is indicated. Many forms of physical therapy and passive motion are dangerous in the postreduction care of the patients. Heat, gentle massage and active motion are the most important procedures to be adopted.

Anderson⁵⁰¹ describes the mechanics of "nursemaid's elbow" as a sudden pull on the extended elbow of a small child which causes anterior dislocation of the head of the radius followed by pain and disability of the arm. The dislocation is slight and can be detected only by roentgen examination of both elbows. Forcible supination while the elbow is bent usually reduces the displacement, and this is often accompanied by a definite click. It is believed that the infantile radial head is pulled through the orbicular ligament, since in early childhood there is not a definite radial head to resist this pull. There is no definite ligamentous tear, hence symptoms are relieved immediately after reduction.

Fractures of the Forearm—Blount, Schaefer and Johnson⁵⁰² give a rather comprehensive discussion of fractures of the forearm in children under 12 years of age and make a plea for conservative management, with the statement that open reduction for fractured forearms of children is difficult to justify. They present several cases of excellent functional results in fractures in which there was fair alignment but unusually pronounced lack of apposition. In conclusion they give the following summary: "(1) Fractures of the forearm in children are different from those in adults and should be differently treated. (2) There is a definite hazard associated with open reduction of fractures of the forearm in children. (3) Except at the elbow, open reduction of fractures of the forearm is difficult to justify in children. (4) Greenstick fractures of the middle third should be reduced by completing the fracture in the interest of maintaining alignment. (5) The radial head should never be removed in a child. (6) If conservatively treated, most epiphyseal fractures of the distal end of the radius will heal without disability." [ED NOTE—This is an interesting discussion of an ever present problem. The fact that alignment and apposition do not necessarily have to be perfect should not be used as an excuse for poor treatment of these fractures. In the experience of some open reduction when indicated in the markedly displaced fractures has not given the disastrous results reported by the authors.]

Fractures of the Lower End of the Radius and Ulna—Darrach⁵⁰³ surveys all the features of the problem of fractures of the wrist and discusses the anatomy, pathology, diagnosis and treatment. For comminuted fractures of the lower end of the radius he advises placing one wire through the base of the second, third and fourth metacarpals and another wire through the ulna just distal to the coronoid. After traction has been applied and the fracture reduced, both wires are incorporated in a plaster cast. [ED NOTE—This is an excellent brief summary of the subject.]

Sever⁵⁰⁴ studied 199 cases of Colles' fracture roentgenologically before and after reduction. Measurements of the degree of dorsal or volar angulation of the distal fragments were made. The group included simple fracture with little or no displacement to severe comminuted fracture with considerable displacement. In 36 cases the angulation was reduced to 90 degrees, in 24 cases there was an average

501 Anderson, S. A., Jr. Subluxation of Head of Radius. *Pediatric Condition* South M J 35 286-289 (March) 1942

502 Blount, W. P., Schaefer, A. A. and Johnson, I. H. Fractures of the Forearm in Children. *J. A. M. A.* 120 111-116 (Sept. 12) 1942

503 Darrach, J. W. Colles' Fracture. *New England J. Med.* 226 594-596 (April 9)

504 Sever, J. W. Colles' Fracture. A Study of X-Ray Films Before and After Reduction. *New England J. Med.* 226 790-794 (May 14) 1942

residual deformity after reduction of — 83 degrees. Thus in 60 cases, or 39 per cent, the reduction was not satisfactory according to roentgenologic standards. In 92 other cases the average postreduction angle was plus 109 degrees. Individual values varied from + 5 to + 30 degrees. In cases in which the reduction was performed by a surgeon of experience and skill, generally an excellent anatomic result was found. The author makes a plea for more perfect reductions, correcting dorsal displacement and radial deviation, and for more careful preoperative and postoperative roentgenologic interpretation, including angular measurements.

Ruhlin⁵⁰⁵ discusses in detail the etiology and pathology of the condition which most commonly occurs in association with fractures of the lower end of the forearm and is probably due to rupture of the radioulnar triangular ligaments, which permits the lower end of the ulna to separate from the lower end of the radius and cause a disfiguring deformity with occasionally pain and dysfunction. He mentioned no less than twelve different operative techniques, stating that each operator seemed to have his own technique, there being no standard accepted method for open fixation. The plan for operation is essentially either to obtain solid union between the radius and the ulna at the distal end, with or without resection of the ulna above the point of union, or, secondly, to obtain fixation by some type of fascial sling or loop between the ulna and the radius. Results are not uniformly good, and operation should be reserved for patients with a high degree of disability and pain. Nine cases were recorded at the University of Iowa Hospital, 4 of the patients came to operation and the other 5 responded to conservative treatment, consisting of fixation by a wristlet and physical therapy. [ED NOTE—It would appear obvious from the multitude of operative plans suggested that none of them are entirely satisfactory. The author does not mention the fact that the radius is often foreshortened and there is actually a comparative lengthening of the shaft of the ulna which will require resection of some portion of the ulna in order to restore a normal relationship in length between the radius and the ulna. This condition is much more common than the reports in the literature would seem to indicate. We have had 3 successful results with fascial transplants, modified Elhason technic.]

Milch⁵⁰⁶ gives a logical and comprehensive discussion of a so-called dislocation of the lower end of the ulna. He points out that the name of the deformity is a misnomer, that the ulna is the fixed point of the wrist to which the carpus and radius are attached by the ligaments of the wrist joint. He includes a whole group of conditions which have a wide variety of causes which will require similar variety in treatment. Prominence of the head of the ulna may be caused by (1) the triangular fibrocartilage, (2) the ulnar collateral ligament, (3) rupture of the radioulnar ligaments, (4) actual deformity of the bones of the forearm, (5) disproportion in length of the bones of the forearm and (6) enlargement of the ulnar head itself. From the standpoint of treatment, types 1, 2 and 3 are classified together as due to injuries of a ligament and are best treated by repair of the involved or damaged ligament. In early stages this can be done by operation on the ligament itself, and later the fascial loop operation is the treatment of choice. The author emphasizes that if the condition is caused by actual deformity of the osseous structures, in either actual deviation of either bone of the forearm or disproportion in length of the bones, or by disease of the ulnar head, it is imperative that the bony deformity be corrected before any repair of ligaments is attempted. Repair of ligaments can result only in failure if there is a basic maladjustment between the radius and the ulna. In most cases correction of the bony deformity will in itself correct the condition and repair of a ligament will not become necessary. The author makes a plea for careful study of these conditions to avoid needless sacrifices of the head of the ulna, since repair of ligamentous structures to the intact ulnar head is much more essential in cases in which the condition is caused by damage of a ligament. He emphasizes repeatedly that the lower end of the ulna is the fixed point at the carpus and that sacrifice of this point can result only in imperfect function at best.

505 Ruhlin, C. W. Subluxation of Distal End of Ulna, *J. Maine M. A.* **33** 197-200 (Sept.) 1942.

506 Milch, H. So-Called Dislocation of the Lower End of the Ulna, *Ann. Surg.* **116** 282-292 (Aug.) 1942.

[ED NOTE —This is an excellent article and merits careful study by any one facing this problem]

Fractures and Dislocations of the Bones of the Hands and Feet —Farquharson⁵⁰⁷ believes that the main cause of delayed union in fractures of the carpal navicular is shearing strains to which the fracture is subjected by movement at the wrist joint. He has devised a special splint to give continuous immobilization in these fractures. The splint is shaped to the contour of the hand and wrist and consists of a light metal framework with an adjustable band of soft aluminum which encircles the hand and allows free flexion of the fingers. The author states that in the cases in which the splint has been employed progressive union has taken place. [ED NOTE (L D B) —The author has described a practical splint. The value of the paper is in its warning against incomplete immobilization.]

Fractures of the os triquetrum are believed by Fairbank⁵⁰⁸ to be much more common than was previously supposed. Of 11 fractures of this type that were treated, 10 were small chip fractures and 1 was a complete fracture through the middle of the bone without displacement. All were due to a backward fall on the outstretched hand, in 1 instance in volar flexion and in 10 in dorsiflexion. All the patients were soldiers, and their ages varied from 23 to 37 years. Examination showed a stiff, weak, painful wrist with pain, swelling and tenderness over the dorsum of the os triquetrum. Dorsiflexion and ulnar deviation produced pain. On roentgen examination, all were visible in the lateral but invisible in the antero-posterior view. The oblique view is most important, as it shows whether the chip is from the os triquetrum or the lunate bone. No attempt was made at reduction, as the displacement was never pronounced. Four patients were treated by plaster fixation for a time varying from four to ten weeks. The remaining 7 were placed in strappings of elastic adhesive tape (elastoplast) and were back on full duty in one to twenty-eight days, the average being ten days. Union took place in all cases, although in 1 it required twelve months. With the chip fractures, prognosis is excellent and recovery rapid. Immobilization does not seem necessary for bony union. The avulsion fractures are more serious and require longer periods of immobilization. Minor symptoms may persist for many months, but they do not interfere with the activities of the patient.

Ferreira and Carranza⁵⁰⁹ report 8 cases of fracture of the base of the first metacarpal bone and state that the typical Bennett fracture has an oblique direction. They divide the fractures of the base of the first metacarpal into five types, as follows: (1) total extra-articular fracture (transverse or oblique), (2) mixed extra-articular fractures with an intra-articular fragment, (3) articular fractures of the Bennett type, (4) articular fractures of the Rolando type (Y shaped), (5) partial articular fractures which are H shaped and have four fragments, three of them intra-articular. They point out the importance of accurate reduction and state that the purpose of reduction is to avoid limitation of the four fundamental movements of the thumb. They have found that the best results can be obtained when traction is exerted in the direction of a line from the center of the fold in the elbow to the styloid apophysis of the corresponding radius.

Fitte⁵¹⁰ suggests a technic for treatment of semilunar dislocations. Local procaine hydrochloride anesthesia is used, and one-quarter hour later continuous traction is applied to the fingers by means of the Finocchetto apparatus with 15 Kg of weight for ten to fifteen minutes. A roentgenogram is then taken, which may in some cases show that spontaneous reduction has occurred. A plaster cast is applied to maintain the reduction. Good reduction was obtained in all 8 cases by this technic. An improvised traction apparatus is described, for use by physicians.

507 Farquharson, E. L. Splint for Fracture of Carpal Navicular, *J. Bone & Joint Surg.* 24 922-924 (Oct.) 1942

508 Fairbank, T. J. Chip Fractures of Os Triquetrum (Carpal Cuneiform), *Brit. M. J.* 2 310-311 (Sept. 12) 1942

509 Ordonez Ferreira, H., and Martinez Carranza, H. Bennett Fracture. *Casa. Biol. y Trab., Soc. de Cir. de Cordoba* 2 263-277, 1941

510 Fitte, M. J. Therapy of Luxation of Semilunar Bone and of Second Row of Carpus. *Bol. y Trab., Acad. Argent. de Cir.* 26 534-539 (July 22) 1942

who do not have the Finochetto appliance [ED NOTE—In isolated dislocations of the semilunar bone one editor (H E C) feels that no technic is superior to early diagnosis followed by early reduction by the thumb pressure and manipulative technic]

Gebhard⁵¹¹ describes a method for the treatment of fractures of the metatarsal bones in which no fixation is used. It consists of application of an anterior bar on the shoe, the bar being placed $1\frac{1}{2}$ to $1\frac{3}{4}$ inches (3.8 to 4.5 cm) obliquely to the metatarsal heads in front of the heel, the location being determined by having the patient bear weight with the foot in a shoe over a broom handle and the point at which weight bearing is free of pain is where the bar is attached. The bar should be high enough to keep the ball of the foot from reaching the floor. Gebhard states that follow-up roentgenograms revealed uniformly good results. The theory of treatment is that with the bar under the arch of the foot the toes tend to reach for the ground and so arch the metatarsals into normal position. He states that the patients were highly satisfied and that they were able to return to work within a couple of weeks from the time of injury. The method was used in cases in which no more than four metatarsals were broken. [ED NOTE—No roentgenograms are shown, no case reports are given, and no contraindications to the method are mentioned. The recommendation of this method would better be supported by roentgenograms and detailed case reports. The author should be urged to present his cases in detail to permit further study of the method.]

Fractures of the Pelvis—Dewitt⁵¹² reports a case of fracture of the acetabulum with medial displacement of the head of the femur. Perfect reduction was secured by skeletal traction exerted longitudinally and by a lateral pull secured through the use of an eye screw fastened into the greater trochanter. Nevertheless, three years later there were many degenerative changes in the head of the femur, due doubtless to the circulatory damage which accompanied the original injury. [ED NOTE—In any case of injury of the hip with dislocation of the head of the femur, it is proper to assume that the nutrition of the head is seriously impaired. Therefore, prolonged protected weight bearing for many months should be a routine recommendation. The author's method of reduction would appear to be more comfortable than most of those generally used.]

Furey⁵¹³ reports 96 fractures of the pelvis, resulting for the most part from great violence. Eighty-six involved the region of the obturator ring. Sixty-seven were posterior fractures of the pelvic ring. Close study of the bodies, wings and foramina of the sacrum gave clues leading to the discovery of many of the more obscure fractures. Excellent roentgenograms are essential, and in many cases one has to reexamine the patient carefully in the x-ray department when his condition improves, instead of relying on a portable film, which shows only the obvious fracture of the obturator ring. The literature reveals reports of from 5 to 30 per cent of posterior pelvic fractures. This contrast with the 70 per cent incidence in this series indicates, according to the author, that such fractures are being missed. The large number of fractures of and about the sacrum, occurring mostly as a result of automobile accidents, is undoubtedly due to the tremendous force involved in such accidents. The author believes that closer study of the sacrum and better detail in the roentgenograms will undoubtedly lead to discovery of many more such fractures.

Fractures of the Femur—Van Gorder⁵¹⁴ reviews the modern treatment of fractures of the femur and proposes the following standard form of treatment. For fractures of the femoral neck, a cannulated Smith-Petersen nail, for intertrochanteric fractures, Russell traction, although operative treatment in competent

511 Gebhard, U E. Simple Treatment for Fractured Metatarsals, *Indust Med* **11** 157 (April) 1942.

512 Dewitt, R F. Method of Treatment Used in Fracture of Acetabulum, *J Bone & Joint Surg* **24** 690-691 (July) 1942.

513 Furey, W W. Fractures of the Pelvis, with Special Reference to Associated Fractures of the Sacrum, *Am J Roentgenol* **47** 89-96 (Jan) 1942.

514 Van Gorder, G W. Fractures of the Femur, *New England J Med* **226** 526-530 (March 26) 1942.

hands is being used successfully more and more, for low supracondylar fractures open reduction or, if that is impossible because of comminution of the fragments skeletal traction from the tibial tubercle through the knee joint in conjunction with use of a Thomas splint and a Pierson attachment, and for fractures of the shaft of the femur, Russell traction for fractures of the upper third and skeletal traction with a Thomas splint and Pierson attachment for fractures of the middle or lower third. Under war conditions, the insertion of fixation pins above and below the site of fracture, reduction of the fragments and incorporation of the pins in a plaster cast or in a Roger-Anderson steel side bar seems to be the most practical form of therapy, since it permits hurried evacuation.

For children up to the age of 6 years overhead traction with adhesive tape applied to the skin is the method of choice. For children over 6 years, Russell traction or traction with adhesive plaster applied to the skin in a Thomas splint followed by use of a plaster cast, is recommended. In hospitals fully equipped for operative procedures on all kinds of fractures, where fracture services are established and the treatment of fractures is considered a specialty open reduction with internal fixation is the ideal form of treatment of all fractures of the femur in adults.

Fractures of the Patella—Dobbie and Ryerson⁵¹⁵ report 21 cases of complete excision of the patella as treatment for transverse and comminuted fractures with excellent results. A good summary of the history of treatment of fractures of the patella is contained in the article. Indications for total removal of the patella are all simple fractures with separation of fragments that require open operation and all compound fractures. Either a transverse or a longitudinal incision is employed. After excision of the entire patella the lateral and medial tendinous expansions are sparingly debrided and sutured. Then the central portion at the site of the patellar excision is sutured edge to edge.

Immediately after the operation the patient is encouraged to move freely about in bed, and on the third or fourth day he is allowed out of bed and encouraged to walk, with or without the aid of a cane according to his desires. Between the seventh and the tenth day the wound is dressed for the first time, stitches are removed and all dressings are discarded. Active flexion and extension exercises are begun. By the end of the second week the patient ambulates well without aid of any sort. The patient is then discharged with instructions to do a considerable increasing amount of walking daily and is encouraged to walk up and down stairs as much as possible. At the end of six to eight weeks he is able to walk long distances, negotiate stairs and in many instances return to laborious work. Of the 16 patients who could be followed, all had excellent results from three to forty-one months later on the basis of the strictest standards. Dynamometer tests of the power of the quadriceps muscle revealed no impairment of muscle power following recovery, and in many cases the dynamometer reading was 3 to 8 pounds (1.5 to 4 Kg.) greater in the affected limb.

Postoperative roentgenograms disclosed some attempt at regeneration of the patella as evidence of calcific shadows. In 1 case in which the patient died of a pulmonary embolus seven weeks postoperatively sections showed excellent primary union at the suture line with proliferation of fibrous tissue and numerous confluent, glistening hard areas of young growing bone.

movement and the power are in no way inferior to those displayed in the opposite, intact limb [ED NOTE—The results have been observed by one of the editors (L D B) They are excellent Can equally good results be obtained by excision of the least useful fragment and repair of the soft parts?]

Thomson⁵¹⁶ discusses the three types of treatment of fractures of the patella (1) restorative treatment, (2) excision of the patella, and (3) removal of loose fragments with plastic repair of the patellar tendon He collected 554 instances of use of the third type from leading fracture surgeons by the questionnaire method He advocates the removal of all but a single attached fragment of the patella in either the proximal or the distal pole and suturing of the patellar tendon to this remaining fragment He believes that the patella is necessary for the mechanical advantage it produces by means of its pulley action He points out that the osseous reparative quality of the patella is poor

He concludes that the removal of all fragments except one pole of the patella reduces the problem from one in which an effort is made to obtain a union of fragments of bone that have little osteogenic property to one in which only union of soft tissue is involved, without loss of fulcrum stability of the patella or of buffer protection to the exposed condyles of the femur By accomplishing this, the period and the amount of disability are reduced [ED NOTE (L D B)—The author should be commended for the zeal and enthusiasm with which he has undertaken his crusade against mismanagement of this type of fracture]

Wass and Davies⁵¹⁷ summarize the views of Brooke on excision of the patella for a simple transverse fracture and review the recent literature, showing that the consensus is against adoption of this procedure as a routine measure Unsatisfactory results were obtained in 8 cases and are described in detail The incidence of ossification in the quadriceps tendon following the operation is discussed The authors suggest that the patella should not be excised for simple transverse fractures with separation Indications for excision of the patella are comminuted fractures with separation, compound fractures and selected cases of patellofemoral arthritis following malunited fractures [ED NOTE—The ideas presented by the authors coincide with the opinions of most of the editors]

Fracture of the Tibia—Mathewson⁵¹⁸ reports on 132 spiral fractures of the tibia 74 being treated by open reduction under traction in a Böhler frame and application of one stainless steel wire loop He is opposed to the two pin method of treatment and to plating, because he feels that the incidence of nonunion is greater with these methods His method consists of inserting a pin in the os calcis and applying longitudinal traction in a Böhler frame with the knee in flexion Traction is applied to overcome shortening, and any rotary deformity is corrected The skin in the operative field is then prepared and the leg draped On exploring the site of fracture, it is almost always possible to obtain a perfect reduction by a simple manipulation in the frame Drill holes are made at an angle through the fragments in such a way that the upper portion of the loop is in the proximal portion of the distal fragment and the lower end of the loop in the distal end of the proximal fragment This steel sling thus prevents shortening A light dressing is applied over the wound, and a long leg nonpadded cast is applied, the leg part being put on while the limb is still in the Böhler frame, with the pin in the os calcis incorporated The postoperative care consists of immediate motion of the toes and contractions of the quadriceps muscle In two weeks the cast is removed the sutures are taken out and a new nonpadded long leg walking cast with a walking iron is applied The patient is encouraged to bear full weight on the affected limb, within the limits of pain After six weeks the cast is removed, and usually bony union has occurred Physical therapy is then started

516 Thomson, J E M Fracture of the Patella Treated by Removal of the Loose Fragments and Plastic Repair of the Tendon, Surg, Gynec & Obst 74 860-866 (April) 1942

517 Wass, S H, and Davies, E R Excision of the Patella for Fracture, Guy's Hosp Rep 91 35-57, 1942

518 Mathewson, C, Jr Spiral and Oblique Fractures of the Tibia, Am J Surg 55 295-308 (Feb) 1942

In the 74 patients treated by open reduction and wiring, all operative wounds healed per primam with the exception of 2. Both were opened and packed with petrolatum gauze, and in both healing was retarded but solid union was present at the end of five months. The average period of immobilization in plaster was from eight to twelve weeks, the average total period of disability, fourteen weeks. Nonunion occurred in 1 patient, a 37 year old woman who was discharged sixty-seven days after operation with "good union" and "good functional results." She returned two years later with nonunion at the site of fracture. After removal of the steel wire and drilling of the site of fracture, prompt healing occurred.

Of the remaining 68 patients treated by close reduction, 11 had nonunion. Three of them had been treated by means of simple casts and 8 by the use of two pins, one above and one below the site of fracture. The author believes that the two pin method often maintains distraction, which is a frequent cause of nonunion. [ED NOTE (L D B) —The author's opinion as to the distraction caused by the two pin method is in keeping with that of some of the editors. Obtaining union at the end of six weeks after open reduction of a fracture of the shaft of the tibia is unusual.]

Raymond⁵¹⁹ reports a case of avulsion of the tibial tubercle in a 15 year old boy following a severe injury. The avulsed fragment was replaced and anchored with silk sutures. The author states that only a few cases of such a lesion have been reported and that good results can be obtained only by replacing the fragment by operation.

Pease⁵²⁰ describes the use of beaded wires for lateral traction on spiral and oblique fractures of the tibia, and describes their advantages in certain selected cases. He recommends use of a specially designed lateral bar incorporated in the cast, to which the traction nuts are applied, in order to prevent direct pressure of the nuts against the side of the cast.

Wilson and Cantwell⁵²¹ report 89 cases in which fractures of the leg were treated by the use of Steinmann pins through the calcaneus and through the upper end of the tibia. After reduction of the fracture, both pins were incorporated in a plaster cast. Early weight bearing was allowed. [ED NOTE —If reduction cannot be maintained otherwise, this method secures fixation. It is hard to see the advantage of using a walking iron a few days after a fracture of the tibia or fibula. No proof exists that this hastens healing, and it would seem likely to cause some change of position of the fragments in the first few weeks even with this relatively secure fixation.]

Gerwig⁵²² describes an apparatus for maintaining continuous traction for comminuted, spiral or oblique fractures of the tibia and fibula. Countertraction bars are incorporated in the cast, and as a modification of several previously described apparatus traction is applied from the heel through a spring to an extension bar incorporated in the back of the cast. [ED NOTE —The apparatus seems to be entirely satisfactory for this type of fixation. It is particularly emphasized that the patient is not confined to bed and has a considerable degree of mobility. Treatment by this method is extremely limited, since most orthopedic surgeons agree that some type of fixed traction is more efficient and comfortable and gives better immobilization with the average compound fractures.]

Child⁵²³ describes in great detail the development of gangrene in the lower extremities following fracture of both bones of the leg, which had had a severe contusion of the soft tissue. He reviews the literature and finds that only 40

519 Raymond, S W. Avulsion Fracture of Tibial Tubercle, *Illinois M J* **81** 476-477 (June) 1942

520 Pease, C N. Beaded Wires in Closed Reduction in Fractures of Leg, *Surg, Gynec & Obst* **75** 647-651 (Nov) 1942

521 Wilson, M J, and Cantwell, A R. Double Pin Method in Treatment of Fracture of Tibia and Fibula, *Am J Surg* **56** 445-447 (May) 1942

522 Gerwig, W H, Jr. Mobile Skeletal Traction for Severe Leg Injuries, *Mil Surgeon* **91** 213-217 (Aug) 1942

523 Child, C G. Noninfective Gangrene Following Fractures of Lower Leg, *Ann Surg* **116** 721-728 (Nov) 1942

such cases have been reported since 1850. The anatomy of the leg is discussed in detail, particularly in regard to the arterial blood supply. The suggestion is made that the bifurcation of the popliteal artery into the anterior and posterior tibial arteries is a particularly vulnerable location, owing to the fixation of the artery to the soft tissue at this point and the proximity of the anterior tibial artery to the upper portion of fibula. He notes that the development of gangrene is gradual, over a period of several days, and that when it once occurs amputation of the extremity apparently is the only remedy. The cases reported present no significant etiologic factor, in age or degree or location of injury. In many of them gangrene developed in the absence of any possible constriction. The patients were treated without plaster support. Child suggests that the cause is probably thrombosis of the anterior or posterior tibial artery or both, due to damage to the intima of the vessel, which causes the development of the gradually enlarging thrombus. He thinks this more probable than an actual occlusion of the vessel at the time of injury. Treatment should be promptly instituted. He suggests heparinization of the patient and relief of any internal pressure by evacuation of the hematoma and other appropriate measures. Repair of the vessel should be done if possible, and some form of sympathetic block must be instituted. [ED NOTE—The suggestion that gangrene is due to intimal damage of the vessel seems hardly likely, since intimal damage must occur in a multitude of cases and not go on to thrombosis or to gangrene. His suggestion that this condition be looked for is well made, since if any treatment is to be successful it must be instituted early. It is noted that in the cases reported all but 2 patients had amputations and only 1 obtained a useful extremity.]

Burns and Young⁵²⁴ analyzed records of 27 patients with simple fractures treated from 1927 to 1930 at St. George's Hospital. Back and side splints were applied for four weeks, during which time massage was given and the joints were gently moved. Then a plaster cast was applied, and the patient was allowed to get about on crutches without weight bearing until union was firm enough for the plaster to be taken off. The average time of union was eleven and one-half weeks. For 95 patients with simple fractures treated in 1941 and 1942 at Botley's Park Orthopaedic Center plaster was applied at the beginning over a thin layer of wool, and the average time of union was fifteen and one-half weeks. A third group of patients, treated by internal plating and insertion of a cross screw at right angles to the other screws without external fixation, had full movement from the start, and there seemed to be firm union by bone in twelve weeks. The authors conclude from their studies that early weight bearing favors union and that traction or use of two transfixation pins for more than a short time hinders union. They suggest that a certain amount of movement in the early stage may be a stimulus to formation of callus and that the much greater immobilization that plaster gives may eliminate this stimulus in the long bones at any rate. They conclude that until a better method is found of obtaining early union without the danger of sacrificing anatomic reduction, the best treatment is plating with a cross screw at right angles to the other screws. [ED NOTE—They base their opinion on the cases of 12 patients so treated.]

Dislocations of the Ankle—del Sel⁵²⁵ describes a pure tibiotarsal dislocation without fracture in a woman of 31. He discusses the rarity of this injury and points out that the prognosis is somewhat influenced by the common presence of lesions of tendons. He states that the mechanics of the production of these dislocations is difficult to explain and discusses various theories as to the muscular action that brings about the dislocation. [ED NOTE—One of the editors (H. E. C.) has treated and reported on 2 patients with complete dislocations of the ankle without a fracture. Both patients had excellent functional results. One

524 Burns, B. H., and Young, R. H. Time of Union in Fractured Tibia, *Lancet* 2:299-301 (Sept. 12) 1942.

525 del Sel, J. M. Pure Tibiotarsal Luxation, *Rev. ortop. y traumatol.* 12:27-32 (July) 1942.

patient had a complete posterior dislocation of the ankle The second ^{52a} had a complete internal lateral dislocation]

Fractures of the Astragalus—Boyd and Knight ⁵²⁶ have studied 58 cases of fracture of the astragalus, and their report is based on this experience The astragalus possesses an inadequate blood supply, and it is practically covered with articular cartilage Because of the various articulations about the bone, accurate reduction of its fractures is important Open reduction with fixation of fragments is often necessary If the proximal fragment is dislocated, subastragalar fusion should be done to prevent later deformity of the foot For extremely comminuted fractures, astragalectomy is the operation of choice [ED NOTE—The authors present an excellent classification of these fractures]

As a result of study of a series of 30 cases of fracture and fracture-dislocation of the astragalus, Schrock, Johnson and Waters ⁵²⁷ recommend the following procedure in case astragalectomy seems essential an immediate calcaneotibial arthrodesis, in which, if available, a portion of the astragalus is used as a surface adaptor or wedge to decrease the amount of shortening in the extremity The tibia is placed with its anterior margin in the vertical plane of the calcaneocuboid joint, and the foot is placed in the optimum position for the individual patient In males, a minor degree of equinus (5 degrees) may be desirable, in females, the degree of equinus rarely is in excess of 15 degrees The blood supply to the astragalus is relatively poor, and transcervical fractures interrupt this blood supply Revascularization is slow, and hence there is a high incidence of aseptic necrosis There is the necessity of early anatomic reduction by manipulation or by open reduction, with or without internal fixation, as indicated by the stability of the fragments The articular dome of the body must be smooth and the calcaneo-astragaloid surfaces accurately apposed

In the cases in which subastragalar contact is faulty, immediate subastragalar arthrodesis is indicated, to obtain earlier function and to prevent pain in the foot on weight bearing Tibioastragalar arthrodesis is indicated when there has been demonstrable damage to these cartilage surfaces For compound dislocations with minor fractures, careful cleansing and detailed debridement, coupled with local and general administration of sulfonamide derivatives, give a greater chance for successful conservative surgical treatment For compound, severely comminuted fractures, the same technic gives a reasonable chance for immediate reconstruction With certain markedly comminuted simple or compound fractures of the astragalus, reduction and retention of the multiple fragments are impossible Astragalectomy or calcaneotibial arthrodesis seems a necessity Calcaneotibial arthrodesis would appear to offer a more satisfactory result than astragalectomy

Fractures of the Calcaneus—Gray ⁵²⁸ states that the modern method of treating crush fractures of the os calcis consists in reduction by traction and compression, followed by long immobilization in plaster The articular facets for the astragalus cannot be completely and accurately restored by this or any other method In addition, this method promotes stiffness of the foot, incurs the risk of sepsis and encourages compensation neurosis Conservative treatment leaves a comfortable and mobile foot and avoids the danger of sepsis Lateral spread if considerable is reduced with a hand clamp, otherwise no attempt at reduction is made The patient is confined to bed, weight bearing being forbidden but early function encouraged, until the disappearance of deep tenderness shows that adequate consolidation has taken place This takes two to three months Alternatively the foot is immobilized for the same period in a plaster cast These methods were successful in 20 of 23 cases [ED NOTE (L D B)—The author's end results are rather unusual for this fracture]

^{525a} Conwell, H E Complete Compound Dislocation of Ankle Joint Without Fracture, J A M A **108** 2035 (June 12) 1937

⁵²⁶ Boyd, H B, and Knight, R A Fractures of Astragalus, South M J **35** 160-167 (Feb) 1942

⁵²⁷ Schrock, R D, Johnson, H F, and Waters, C H Fractures and Fracture-Dislocations of Astragalus (Talus), J Bone & Joint Surg **24** 560-573 (July) 1942

⁵²⁸ Gray, C H Crush Fractures of Os Calcis, Lancet **1** 106-108 (Jan 24) 1942

Dieterle⁵²⁹ describes a method for treatment of fractures of the calcaneus. In his discussion of compression fractures with alteration in contour, he emphasizes the importance of the salient angle, namely, the angle of intersection of two lines projected on the upper edges of the superior processes. He recommends postponement of reduction until after swelling is reduced, ten days or so, and then the use of skeletal traction. He emphasizes the importance of accurate reduction and the necessity for arthrodesis of the subastragaloid joint in the case of painful weight bearing. In discussing skeletal fixation he states that a window should be cut in the cast for inspection of the pin. [ED NOTE—One editor (H E C) finds considerable disagreement with Dieterle's view that reduction should be postponed for a week or ten days while one is waiting for reduction of swelling. His idea of cutting a window for inspection of the pin is certainly open to argument.]

Miller⁵³⁰ gives a brief but adequate discussion of fractures of the os calcis. He mentions the eight types suggested by Böhler, emphasizing that for practical purposes the fractures can be divided into two groups—those which involve the joints and those which do not. He indicates that a good pair of hands and good surgical judgment are of more importance than many of the commercial machines on the market. He emphasizes the necessity of traction in several directions while the reduction is being carried out and application of a carefully molded plaster cast. He makes a plea for careful and accurate reduction in order to minimize postoperative pain. He suggests that in many cases arthrodesis will become necessary to reduce pain. [ED NOTE (L D B)—These conservative views from one who has such a thorough knowledge of the foot are worthy of note.]

Gamm⁵³¹ reports the only case yet recorded of an arteriovenous fistula in the anterior tibial artery which resulted from the use of a Steinmann pin. A seaman treated for a fracture of the calcaneus had had a pin inserted through the lower third of the tibia. Four months later a pulsating mass developed over the anterior aspect of the tibia, which was found to be due to a communication between the anterior tibial artery and vein. [ED NOTE—It is queer that this complication should not occur more often, in view of the wide use of Steinmann pins in fractures of the leg.]

Bankhart⁵³² states "The results of the treatment of crush fractures of the os calcis are rotten. They bear no relation to the accuracy with which the fractures are reduced." He expresses the belief that the best result is to be obtained after a fracture of the os calcis involving the subastragalar joint is a completely stiff but painless foot of good shape, and he recommends a complete triple arthrodesis as a primary measure. A slight modification in the operative procedure is offered in that a short longitudinal incision is first made on the inner side of the foot over the scaphoid for excision of the scaphoid and removal of the cartilage from the head of the astragalus and the base of the cuneiform bone. The usual incision is then made on the outer side of the foot for the calcaneocuboid joint and the subastragalar joint.

Fractures of the Spine—Snyder⁵³³ reviews the literature on "shoveler's fracture" and notes that few cases have been reported in the American literature, which, in view of the frequent reports in the foreign literature, indicates that physicians in the United States are overlooking this injury to the spinous processes. He makes a plea for roentgen examinations at several angles and careful study of the films, since the injury when overlooked seems to result in continued disability. He describes the mechanism of the fracture of the spinous processes and states that the injury may be preceded by degeneration of the bone. [ED NOTE—

529 Dieterle, J O. Fractures of the Os Calcis, Wisconsin M J **41** 662-666 (Aug) 1942

530 Miller, O L. Fracture of the Os Calcis, Tr A Surgeons South Railw Syst (1941) **1** 7-11, 1942

531 Gamm, K E. Arteriovenous Fistula, J A M A **119** 134-135 (May 9) 1942

532 Bankhart, A S B. Fractures of the Os Calcis, Lancet **2** 175 (Aug 15) 1942

533 Snyder, C H. Shoveler's Fracture ("Schipperkrankheit"), J Michigan M Soc **41** 847-849 (Oct) 1942

Early diagnosis of this injury prevents disabilities. The treatment is simple, consisting of strapping and limitation of function.]

Rogers⁵³⁴ reviews the recent advances in the treatment of cervical fractures and states that open reduction and internal fixation should be added as modern improvements. He reviews the advantages of skeletal traction and describes in detail a method of reducing dislocations by means of a hook passed through the spinous processes. He describes also an operative fusion in which he uses wire and small osteoperiosteal grafts. Of a group of 11 patients, 10 achieved solid fusion in normal alignment. Owing to a technical error in the operation, 1 patient showed evidence of a recurrence of the displacement. Nine of the patients were able to return to work. [ED NOTE—Though laminectomy in the cervical region is a tedious, sanguinary procedure, these results and the accompanying roentgenograms are convincing proof that Rogers' operation is worth while. A great argument in favor of it is the prevention of the troublesome late recurrences of the dislocation.]

Darley, Gordon and Matchett⁵³⁵ report 9 cases of spontaneous vertebral compression fractures in patients with senile osteoporosis. They state that the factors governing osteoblastic activity are inadequately understood but that atrophy of disuse in the sedentary and aged, endocrine imbalance and dietary inadequacies (in calcium, vitamin C or D or protein) are undoubtedly causatively related. Endocrine imbalance centers about estrogen, the decrease of which, as seen in the postmenopausal syndrome, is associated with increased excretion of calcium and phosphorus. Eighty to 90 per cent of osteoporosis occurs in women between the ages of 45 and 70. Low calcium intake is a common contributing cause, but there is no evidence to indicate that extra amounts stimulate osteoblastic activity. Lack of vitamin D impairs absorption of calcium from the intestinal tract. Bone matrix is protein in nature, and long-standing inadequate intake of protein may have an adverse effect. Adequate intake of vitamin C is also essential to the formation of normal bone matrix.

The prophylactic treatment recommended consists of (1) admonition against lifting and straining (however, a sedentary existence should be avoided at all costs, if possible), (2) correction of dietary abnormalities, (3) reduction of weight, and (4) support for the back and abdomen as needed.

Easton and Sommers⁵³⁶ studied roentgenograms taken in anteroposterior and lateral views before and after convulsive therapy of the entire spines of 200 patients treated with metrazol (pentamethylenetetrazol). There was evidence of fracture in 23 per cent. In persons over the age of 55 the incidence was 57 per cent (4 out of 7 patients), and in persons under 21 it was 40 per cent (4 out of 10 patients). The higher incidence in the older group is explained by relatively poor bone density, and the lower incidence in the younger, by the fact that the vertebral column in youth has not attained its full adult strength. All fractures occurred in the dorsal portion of the spine, from the fourth to the eighth vertebra, the fourth, fifth and sixth being the most commonly involved. Multiple fractures occurred more frequently in males than in females, owing to the greater muscular development of the former and the more powerful convulsions produced. The clinical symptoms were much milder than would be expected from the roentgenographic evidences of injured spines.

The authors draw the following conclusions: 1. Routine roentgenograms should always be obtained both before and after convulsive therapy. 2. Kyphosis, scoliosis, arthritis, nuclear change and old fractures are no contraindication to metrazol therapy. 3. Osteoporosis is a contraindication. Prophylactic measures recommended consisted of (1) more careful selection of patients, with avoidance of those under 21 or over 55 and those with osteoporosis, (2) mechanical support

534 Rogers, W. A. Treatment of Fracture-Dislocation of Cervical Spine, *J. Bone & Joint Surg.* **24**: 245-258 (April) 1942.

535 Darley, W., Gordon, R. W., and Matchett, F. Spontaneous Vertebral Compression Fractures Due to Senile Osteoporosis, *Rocky Mountain M. J.* **39**: 193-196 (March) 1942.

536 Easton, N. L., and Sommers, J. The Significance of Vertebral Fractures as a Complication of Metrazol Therapy, *Am. J. Psychiat.* **98**: 538-543 (Jan.) 1942.

of the spine during convulsions by a firm mattress and bed boards, and (3) extension of the spine over a sand bag and holding the shoulders down during convulsions. Spinal anesthesia is not recommended. Curare may be of value and is being tried. When a fracture has occurred, the treatment is a matter of judgment. Usually no treatment at all or about two weeks of rest will suffice. When compression to one half or less of the original height of the vertebral body occurs, the treatment by cast or by Bradford frame is indicated. Many of the patients have been discharged from the hospital and have been gainfully employed for one to two years without any complaints referable to the spine. [ED NOTE (L D B) —Many orthopedic surgeons will not agree with the author's recommendations as to treatment of the fractures.]

Worthing and Kalinowsky⁵³⁷ report that 40 per cent of patients treated with metrazol acquire compression fractures of the vertebral bodies between the fourth and the eighth dorsal level. This localization differs from that of the purely traumatic fractures, which usually occur between the twelfth dorsal and the second lumbar vertebra. In order to determine whether secondary changes develop in the metrazol-treated group, 8 patients who had multiple fractures were followed for two years. Complete healing occurred, with no progressive pathologic changes, no evidence of Kummell's disease, no limitation of spinal motion, no pain and no radiculitis. Of 42 epileptic patients studied for comparison, none had middorsal fractures, 1 had a definite compression fracture of the body of the first lumbar vertebra and 1 had evidence of an old fracture of the spinous process of the sixth cervical vertebra. This difference between the metrazol-treated group and the epileptic group indicated a fundamental difference between artificially and naturally produced convulsive seizures. In persons with tetanus compression fractures identical with those seen in the metrazol-treated group have been reported. The authors offer the explanation that a fully developed generalized seizure always has essentially the same features, the tonic and the subsequent clonic phase. The only difference between artificially produced seizures and spontaneous convulsions is the onset. In metrazol convulsions there is an abrupt onset, with a "first clonic phase," which does not occur in epileptic convulsions. The convulsions of tetanus likewise have an abrupt onset. With electric shock therapy compression fractures are much less frequent than with metrazol therapy. The reason is that there is a latent period without an abrupt onset before the generalization of the seizure. (However, if a high voltage is used an abrupt onset will occur without the latent period and fractures similar to those produced by the metrazol convulsions will develop.) Electric shock therapy is therefore superior to administration of metrazol. By using an improved technic, with extreme hyperextension of the spine in addition to electric shock therapy, the authors were able to treat 60 patients without any fractures developing. The authors conclude that there is no contraindication to shock therapy because of the occurrence of fractures, since they can be successfully avoided and if they do occur have no clinical significance. [ED NOTE—One of the editors (L D B) does not agree with the authors' statement that if the fractures do occur they have no clinical significance. In many cases, owing to the patient's age or to other factors, treatment is contraindicated and the results are poor.]

Fractures of the Jaw—Waldron⁵³⁸ gives a comprehensive discussion of the treatment of the various types of fractures of the mandible. He emphasizes the frequency of multiple fractures about the face and jaws and the necessity for detailed study. He states that in the majority of instances manual reduction can be carried out successfully and can be followed by fixation by interdental wiring, which gives tight apposition at the site of fracture. While he states that many fractures will require some special type of apparatus for fixation, it is his opinion

537 Worthing, H J, and Kalinowsky, L B. Question of Vertebral Fractures in Convulsive Therapy and in Epilepsy, *Am J Psychiat* 98 533-537 (Jan) 1942

538 Waldron, C W. Fractures of the Mandible with Special Reference to the Reduction of Complicated Displacements and Subsequent Immobilization, *Journal-Lancet* 62 228-240 (June) 1942

that 90 per cent of fractures of the mandible or maxilla can be efficiently treated by one or another of the standardized methods of wiring. He discusses the various types of fractures of the mandible, with a detailed description of the simplest type of fixation for each type. He details many methods by which posterior fragments can be secured by traction from the angle of the jaw, such as extraoral fixation with screws and pins, intraoral application of splints and various surgical procedures. The multiplicity of the methods indicates that none of them is entirely successful, and he mentions the many complications resulting from the various types. The problem of partially edentulous mandible bone is discussed in some detail. He emphasizes that if direct surgical fixation is secured it must be in addition to fixation of the upper and lower jaws. He suggests that probably it is not necessary to remove a dislocated head of a fracture condyle, since the result seems to be essentially the same whether the fragment is or is not removed. If both condyles are broken, there is a tendency for the jaw to fall backward, and it is important to pull the jaw forward in order to secure proper alinement of the upper and lower jaws.

Waldron,⁵³⁹ in collaboration with Kazanjian and Parker, presents a review of the various methods of external skeletal fixation for fractures of the jaw, including various modifications of the Roger-Anderson method, using two pins in each fragment, attached to a fixation bar, by universal joints. Many modifications of this method are described in some detail with comments by the authors. The second method of fixation, by skeletal wires transfixing the fracture line passed along the long axis of the mandible, is presented and discussed. Since this article is essentially a review of the literature, it is impossible to review this article in any detail. The authors' summary and conclusions are as follows:

The present methods of skeletal fixation as used by a number of men are the logical refinements of what preceded, and they will undoubtedly go through a further developmental stage until they assume a definite and permanent place in the treatment of fractures of the mandible. There are many possibilities for its employment when used intelligently, but we all fear its misuse in the hands of the overenthusiastic. The illustrations and roentgenograms of many published reports show its use in cases wherein the standard and simpler procedures could have been employed with a greater assurance of a more nearly perfect restoration of the occlusion of the teeth. They state "let us welcome any new method of fixation offered for the treatment of fractures, but we should be discriminating and critical at first, and use it intelligently. Otherwise, failures may not only do harm to the patient, but may also bring disrepute to the method which it does not deserve."

Spanier⁵⁴⁰ describes a modification of a simple splint for fixation of severe fractures of the mandible or maxilla before emergency transportation of the patients to the hospital, where treatment can be carried out. Briefly, the splint consists of a well fitted cap of any sort, which must fit snugly to the head. Wooden tongue blades are fastened together to make a strip about 12 inches (30 cm) long, considerably reinforced. A crossbar of a single tongue blade is made halfway down the strip. The whole is then fastened vertically from the forehead, paralleling the nose and bisecting the face. A pad of cotton is placed under the strip over the forehead. For mandibular fractures the mandible can be pulled forward to the end of this wooden strip either with a wire or with suture material around the teeth, or if necessary through the soft tissue of the chin to hold the chin up and forward. In fractures of the maxilla similar fixation can be obtained by wiring around the teeth and up to the crossbar of the splint. [ED. NOTE—This is an ingenious splint and certainly should provide more comfortable and safe transportation than the ordinary method of fixation.]

Kazanjian⁵⁴¹ comments in general on the difference between civilian injuries to the jaw and war injuries, noting that the war injuries often involve extensive loss of substance, not only of soft tissue but of bone. Their treatment is much more complicated. He emphasizes the importance of early treatment, before scar

⁵³⁹ Waldron, C. W. Skeletal Fixation in the Treatment of Fractures of the Mandible, *J. Oral Surg.* **1**: 59-83 (Jan.) 1943.

⁵⁴⁰ Spanier, F. First Aid Splinting of Broken Jaws, *M. Rec.* **155**: 377 (July) 1942.

⁵⁴¹ Kazanjian, V. H. Immobilization of Wartime, Compound, Commuted Fractures of the Mandible, *Am. J. Orthodontics (Oral Surg. Sect.)* **28**: 551-560 (Oct.) 1942.

formation occurs in the soft tissues, as the best means of securing adequate cosmetic and functional results. The three types of fractures discussed specifically are (1) fractures of the anterior part of the mandible with teeth in the posterior segment, (2) fractures of the lateral part of the mandible with teeth remaining posterior to the injury on one side only, and (3) fractures with a distinct loss of bone. He describes various apparatus for fixation of the fragments and methods for securing small comminuted fragments to the general contour of the mandible. He emphasizes particularly that the methods described were used during the last war and he thinks they are equally applicable in this one. He states that in treating fresh fractures of the jaw, speed, efficiency and simplicity are important, and the fixation apparatus should be applied promptly.

With fractures at the angle of the mandible there is often displacement, and, since the proximal fragment is toothless, there is no secure way of immobilizing the fracture after it is reduced. Converse and Waknitz⁵⁴² have developed an external fixation bar which is attached to pins in each fragment. The entire apparatus can be locked together after reduction, if obtained. In this way, the patient has a movable painless jaw while healing is taking place. With proper precautions the danger of infections about the pins is minimal.

For treatment of fractures of the jaw seen some time after the accident, compound fractures, fractures in edentulous jaws, comminuted fractures near the symphysis, and fractures at the angle of the jaw in which the posterior fragment is displaced into the upper buccal fornix, Brown and McDowell⁵⁴³ have devised a simple, ingenious and effective method of fixation. A Kirschner wire is drilled transversely across the line of fracture, and if necessary an interdental wire is also used to supplement the fixation. This gives immediate comfort, no external bandages or splints are needed, and the results so far have been excellent. The wires are easily removed after four or five weeks, so that there is no persistent disfigurement or danger of late complications. [ED NOTE—These methods are not panacea, neither should a novice use such technic. Serious complications can and do and have occurred in the hands of those who are not experienced with the use of appliances for external fixation.]

Fractures of the Malar Bone—Balkin⁵⁴⁴ gives a description of the anatomy of the malar bone, emphasizing that the so-called fracture of the malar bone is ordinarily displacement, since this bone gives away from its attachments to the surrounding structures. He emphasizes the importance of the fact that the malar bone makes up a considerable portion of the orbit and points out that accurate reposition is necessary. He describes a test of ocular balance to determine vertical displacement and states that any great degree of vertical displacement of the eyeball is indication for replacement, since this muscular imbalance of the eye is apt to be permanent if displacement is extensive. He deplors too much dependence on roentgen examination, stating that in many cases the x-rays do not actually visualize the deformity and that clinical examination is more important. Several methods of elevation of the bone are described, he prefers reduction by use of a tenaculum and direct traction.

Injuries of the Nose—Waldron⁵⁴⁵ in a comprehensive article describes the various types of fractures of the nose. He emphasizes the importance of careful suturing of lacerations and careful lavage of the wound if one is to obtain good cosmetic results. He gives a classification of the types of fractures of the nasal bone, with a treatment for each. He emphasizes the importance of clinical diagnosis. A description of the anatomy of the nose is given as a preliminary to

542 Converse, J. M., and Waknitz, F. W. External Skeletal Fixation in Fractures of Mandibular Angle, *J. Bone & Joint Surg.* **24** 154-160 (Jan.) 1942.

543 (a) Brown, J. B., and McDowell, F. Internal Wire Fixation for Fractures of Jaw. Preliminary Report, *Surg., Gynec. & Obst.* **74** 227-230 (Feb.) 1942. (b) Brown, J. B., and McDowell, F. Internal Wire Fixation of Jaw Fractures. Second Report, with Note on External Bar Fixation, *Surg., Gynec. & Obst.* **75** 361-368 (Sept.) 1942.

544 Waldron, C. W., Balkin, G. G., and Peterson, R. Fractures of Facial Bones in Children, *J. Oral Surg.* **1** 215-234 (July) 1943.

545 Waldron, C. W. Injuries of the Nose, *Minnesota Med.* **25** 258-267 (April) 1942.

treatment He discusses fractures of the nasal septum and comments that many fracture-dislocations of the septum can be reduced promptly and will hold a certain portion of the reduction The majority of them, however, if there is serious displacement, will require a plastic operation, which is better postponed until healing occurs [ED NOTE—This is an excellent and comprehensive article]

Compound Fractures—Macpherson⁵⁴⁶ concludes that the best method of handling war wounds is (1) soap and water cleansing of the skin, (2) debridement, with removal only of devitalized tissue and elimination of pockets and (3) generous application of sulfanilamide followed by a nonocclusive type of dressing Physiologic rest of the part is best gained by the use of a plaster cast, whether the lesion be a fracture or lacerated wound Dressings should be performed as infrequently as possible In times of stress traumatic wounds may be safely treated by the use of sulfanilamide and a sterile dressing with debridement postponed and primary suture postponed for as long as seventy-two hours or perhaps even longer Sulfanilamide in crystalline form which does not have to be sterilized and can be contained in an ordinary salt shaker is the drug of choice, since it is readily absorbed and does not cake in wounds [ED NOTE—One of the editors (L D B) believes that sulfathiazole in small amounts has a higher bacteriostatic effect on staphylococci, remains longer in the wound and is a more efficient drug than sulfanilamide]

Ponseti and Guri⁵⁴⁷ give a comprehensive and instructive discussion of treatment of injuries, particularly compound fractures, during the Spanish civil war They divide the discussion into three divisions (1) treatment on the battle field, (2) treatment in the surgical station, and (3) treatment in the base hospital With regard to treatment on the battle field, it is emphasized that the essential treatment is to provide immobilization and to control bleeding Only superficial cleansing was done, no treatment was attempted for the fracture They note that, although tetanus antitoxin was very useful, anti-gas-gangrene serum appeared to be useless and was seldom used after the first year of the war Prompt evacuation to a hospital train, to a hospital trailer or to a field hospital was recommended A comprehensive discussion of treatment in the surgical station is given, including the general organization of the station Wounds of the extremities are discussed in great detail, particularly their treatment by the closed, or Orr, method versus the open air method It is emphasized that in each method an adequate surgical procedure is the most important factor, and considerable discussion is given as to technic, emphasizing that all traumatized tissue should be removed and that none of these wounds should be closed A general order was issued that no wound requiring débridement should be closed Drainage was instituted with petrolatum gauze or otherwise, and the extremity was immobilized in a plaster cast The difference between the Orr method and the open air treatment (the latter entailing a window in the cast for observation of the wound) is presumed to be understood The authors emphasize particularly the importance of not removing a great deal of bone substance and of not disturbing the area of the fracture any more than necessary They state that it is much more important to do a careful debridement on the soft tissue than it is to meddle with the bone They emphasize again that application of chemicals for disinfecting the wound is useless The third subject of discussion is treatment in the base hospital A rather limited sketch is given as to the various types of after-care Two complications seemed most common development of an abscess in the wound, which required opening for adequate drainage and secondary debridement, and development of secondary hemorrhage, which was a much more serious complication and often required ligation of the main vessel to the extremity and subsequent amputation The authors mention the definite contraindications for the Orr method as being, first, necessity for prompt evacuation of the patient, which would entail his removal from observation for a period of several hours or several days, and, second, the patient's

⁵⁴⁶ Macpherson, J D War Wounds of Extremities Involving Bone, *Hawaii M J* 1 261-262 (March) 1942

⁵⁴⁷ Ponseti, I, and Guri, J P General Principles in the Treatment of Wounds and Fractures in the Spanish War, *Mil Surgeon* 91 39-48 (July) 1942

being received from the battle field late, after infection has actually developed. The authors state that they believe that the Orr method properly carried out, and with regard to its contraindications, is the ideal treatment for persons wounded on the battle field. [ED NOTE—This report is a comprehensive and thoughtful article presenting interesting phases developed from actual experience in the treatment of war injuries. It merits careful study.]

Baker⁵⁴⁸ collected a series of cases from personal communications in which one or more sulfonamide compounds were used in treatment of three groups of conditions: (1) fresh compound fractures, (2) old infected compound fractures and (3) chronic osteomyelitis. In a series of 270 cases of fresh compound fractures, sulfanilamide or sulfathiazole, or a combination of the two, with or without oral administration of one or the other drug, were used. The general impression from this series was that there had been some improvement in the infection rate, but whether this was due to more meticulous surgical technic or to the drug the author is unable to state. The final incidence of severe infections in the 270 fractures was about 10 per cent. The incidence of all infections, either severe or mild, was about 20 per cent. He emphasizes the importance of careful surgical technic and the danger of depending on the sulfonamide drugs rather than on proper surgical intervention. Of old compound fractures with infection, 47 cases were reported, with results that were encouraging but inconclusive because of the small series. Seventy-four cases of chronic osteomyelitis were reported, with good results, only 16 per cent of the patients having final residual infection. The impression was that there was improvement as a result of use of the drug and of the closed method as described by Dickson and Diveley.

Swett⁵⁴⁹ urges caution in the use of sulfonamide compounds in the treatment of war wounds and compound fractures, deploring its use in substitution for careful and adequate treatment. He emphasizes again the danger of relying on chemotherapy and neglecting proper surgical care. He reviews the proper treatment of wounds by debridement and suggests that, while in many cases the wounds may be closed tightly, if there is danger of local accumulation of tissue fluid, drainage should be instituted. In cases of massive destruction of tissue he recommends the use of the Orr technic. He urges the use of plaster rather than splints in order to prevent edema of the tissues and to get adequate fixation to soft parts as well as to bone. [ED NOTE (L. D. B.)—The author's recommendation of the use of plaster fixation is most timely in view of the present enthusiasm for pins and external fixation.]

Orr⁵⁵⁰ states that the principles of modern treatment of a compound fracture must be not a technic, a method or a chemical cure, but a program. If a complete regimen can be applied to every compound fracture situation, which includes immediate reduction of fractured bones and neighboring soft parts, provision of adequate drainage, immobilization in correct position during healing and recovery with the limb in the best length and position for ultimate function, then the wound will take care of itself. He outlines the following procedure. For open infected fractures or fractures requiring surgical operations, immobilize the patient at once in traction and in the best position on the operating table. Do a thorough debridement or drainage operation if necessary. Pack the entire wound open with sterile petrolatum gauze, using no sutures, drainage tubes or antiseptic dressings. Apply an extensive, well fitting plaster of paris cast. Do not change dressings or disturb the cast, the wound, the dressings or the injured part except when there are definite local complications.

The greatest service a surgeon can render to a patient with a compound fracture is to (1) protect him against further injury, (2) restore all the injured parts to correct anatomic relationship at the earliest possible moment, (3) provide

548 Baker, L. D. Sulfonamides in Traumatic and Infected Wounds, *J. Bone & Joint Surg.* **24** 641-646 (July) 1942.

549 Swett, P. P. Chemotherapy in War Wounds and Compound Fractures, *Connecticut M. J.* **6** 713-715 (Sept.) 1942.

550 Orr, H. W. The Treatment of the Infected Wound in Compound Fractures, *S. Clin. North America* **22** 1135-1152 (Aug.) 1942.

adequate drainage for all areas of infected or contaminated tissue, including bone, (4) maintain correct length and position, absolutely, and (5) protect the patient against trauma and infection and even against himself until he has obtained as good a result as his injured parts will permit

The long series of articles by Orr is well combined in the article from the *Surgical Clinics of North America*. He reviews again the history of treatment of wounds and compound fractures. He elucidates the principles on which modern treatment, which is in effect the Orr treatment, is based. He gives in great detail the Orr method of treatment and concludes

My conclusions from twenty years of observation at home and abroad seem to me to be unavoidable. 1 The greatest service that a surgeon can render to the compound fracture patient is to (a) protect him against further injury, (b) restore all the injured parts to correct anatomic relationship at the earliest possible moment, (c) provide adequate drainage for all contaminated or infected tissue areas—including the bone, (d) maintain correct length and position—not relatively, but absolutely—for physiologic function during healing and for use of the injured part upon recovery, and (e) protect the patient against trauma, against infections, and even against himself until he has obtained as good a result as his injured parts will permit. 2 That surgeons now are easily misled by mercurochrome, by maggots, and the sulfa drugs as Lister and his associates were by the mercurial antiseptics, boracic acid, and other chemicals useful as germicides but not cures for wound infection. Chemical irrigation or the antiseptic wet dressing as a cure for infected wounds is as much a fallacy as the carbolic sterilization of the atmosphere. 3 And, that, finally, compound fractures call not for a cure but a program—which I have here ventured to propose.

[ED NOTE—There is no question that the Orr method for treatment has tremendous advantages over older methods, and it is particularly applicable for treatment of war casualties, but it should have combined with it any benefits that are to be derived from the use of the sulfonamide drugs.]

Weil, Whitaker and Rusbridge⁵⁵¹ present a review of their records on the local use of sulfathiazole in the treatment of compound fractures and traumatic wounds. "The greatest value of sulfathiazole is the inhibitor-reducing properties of the drug when applied locally in sufficient amounts at the earliest possible period following the injury to tissues."

Many investigators have found that sulfonamide compounds have little or no detrimental effect on the defensive mechanisms of tissue cells. Wounds heal in normal time without excess serum or scar tissue. Microscopic studies of tissues from skin grafts treated with sulfathiazole showed granulation tissue to appear normally, and there was adequate production of collagen and capillaries. Traumatic wounds should be treated with sulfonamide compounds during the period of contamination, which is agreed to be the first four to six hours. Sulfathiazole is recommended by the authors for use after preliminary culture, immediate debridement and irrigation and complete hemostasis. The wound should be closed without drainage and the part placed at rest by splinting. Patients with osteomyelitis have responded favorably to treatment by placing healthy bone chips in the thoroughly curetted cavity, filling it with sulfathiazole and closing the wound. Immobilization is essential. Few organisms were found in routine bacteriologic studies in cultures of wounds in the first six hours. Positive cultures were obtained from 50.5 per cent of compound fracture wounds and from 39.9 per cent of wounds in the soft tissues. The antibacterial effects of sulfathiazole used locally offset any local irritation or delayed healing which may result. Local application does not present the hazards of oral administration as the rate of absorption is low. In 185 reported cases of compound fractures, traumatic wounds and simple fractures requiring open reduction, 8 deaths resulted, to 1 of which sulfathiazole was felt to be a contributing factor. During the administration of sulfathiazole, renal function should be well balanced and maintained to prevent gross damage to the kidneys. No clinical or electrocardiographic evidences of cardiac change have been noted after administration of sulfathiazole. One patient with subacute bacterial endocarditis received 5,000 grains (300 Gm.) of sulfathiazole without any evidence of cardiac

⁵⁵¹ Weil, G. C., Whitaker, D. W., and Rusbridge, H. W. The Local Therapeutic Effect of Sulfathiazole, *Am J Surg* 55:374-385 (Feb.) 1942.

involvement Observations on the combined use of zinc peroxide and iodine and sulfathiazole have so far been favorable

Frankel and Funsten⁵⁵² report 20 from a series of 28 cases of compound fractures of long bones in which sulfonamide drugs were used locally All the patients were seen within eight hours except 1, who was not admitted to the hospital until twenty-four hours after the injury Routine treatment for compound fractures was used in all the cases This includes (1) immediate splinting, (2) sprinkling the wound with sulfanilamide or sulfathiazole or both, (3) shock therapy, (4) in the operating room, thorough debridement and irrigation, (5) closure of the wound if seen during the eight hour safe period and if no tension is present, (6) sprinkling the wound with a sulfonamide compound before closure, (7) after reduction, application of a snug plaster No infections developed in the 28 cases Nonunion occurred in 1 case of fracture of the humerus in which there was much loss of bone and soft tissue Amputation was advised, but the patient refused The time required for union varied from sixteen to forty weeks with the fractures of the tibia Frankel and Funsten feel that the use of sulfanilamide or sulfathiazole in the wound at the scene of the accident or on the patient's admission to the hospital is of value in preventing infection

Jensen and Nelson⁵⁵³ give a summary of experimental investigations of the effects of sulfanilamide on compound fractures of the ribs in guinea pigs with the wounds contaminated by staphylococci, streptococci or *Clostridium welchii*, or a combination of any two Sulfanilamide has been found to be more effective when implanted locally than when administered systemically in the prophylaxis of wound infection Local application of sulfanilamide will not prevent infections in the presence of massive numbers of contaminating organisms, although it does appear to lessen the severity of infection Devitalized tissue will inhibit the activity of locally implanted sulfanilamide Foreign particulate matter will protect the contaminating organisms against sulfanilamide Sulfanilamide locally administered is more effective against *Cl. welchii* and *Clostridium histolyticum* infections than the systemically administered drug It is of little value against *Clostridium septicum* or *Clostridium oedematiens* with either route of administration In wounds carefully excised gas bacillus infections are rare unless invasion and devitalization of the tissue by virulent aerobic organisms occur (e g hemolytic streptococci) Locally implanted sulfanilamide will protect against this type of infection and consequently greatly reduce the incidence of anaerobic infection Sulfathiazole locally implanted is effective against *Cl. septicum* (Hawking) Polyvalent serum (antitoxin) seems to be the most effective agent against *Cl. oedematiens* (Hawking) Delay of even one hour in local implantation of the drug in wounds contaminated with gas bacilli materially reduces the effectiveness of sulfonamide compounds (Legroux) The antibacterial action of sulfanilamide is directly proportional to the temperature It is suggested that means be used to keep the temperature of a wound at 37 C or above during the first twenty-four to thirty-six hours A summary of clinical results in 212 consecutive compound fractures and 15 compound fracture-dislocations shows (1) The incidence of infection was 4.4 per cent (since 2 of the fractures were due to secondary contamination after infection had been eliminated from wounds, the incidence of infection is really 3.3 per cent), (2) debridement and immobilization remain the basic essentials of successful treatment of compound fractures, (3) with careful debridement and local application of sulfanilamide, internal fixation with vitallium can be safely and perhaps advantageously undertaken (20 compound fractures have been internally fixed without a single instance of wound infection), (4) interrupted fine silk suture is used for buried ligatures and sutures as well as cutaneous closure, (5) prophylactic anti-gas-gangrene serum as well as tetanus antitoxin should be routinely

552 Frankel, C J, and Funsten, R V Compound Fractures Report of Twenty Cases in which Sulfonamide Drugs Were Used Locally Almost Immediately After Injury, *J A M A* 120 1384 (Dec 26) 1942

553 Jensen, N K, and Nelson, M C Local Sulfanilamide in Compound Fractures Experimental and Clinical Evaluation, *Surg, Gynec & Obst* 75 34-48 (July) 1942

used in cases of traumatic wounds even though adequate debridement is done and sulfanilamide powder is implanted in the wounds

The use of sulfanilamide in wounds reduced the incidence of infection in compound fractures treated at the Minneapolis General Hospital from 27 per cent to 3.3 per cent. It reduced the average stay of patients in the hospital from ninety-six and three-tenths to thirty days. Two cases of gas gangrene occurred (less than 1 per cent) in 212 consecutive cases of compound fractures treated with local implantation of sulfanilamide, while 7.3 per cent of the control patients treated without sulfanilamide had gas gangrene. [ED NOTE (L D B) —This report comes from the Minneapolis General Hospital, where the first clinical studies of the local use of sulfonamide compounds as a therapeutic measure were made. It is an excellent summary.]

Epluchage (excision of a war wound in its entire extent) is, according to Fruchand,⁵⁵⁴ the most important curative factor. All other therapeutic procedures are secondary, and even after an initial delay this treatment can be carried out with success. This term implies a much more extensive operation than debridement or enlargement of a wound. The latter has been in vogue since the wars of the sixteenth century, while epluchage was perfected as a method in 1915-1916.

Fruchand does not use suture in any traumatic wound. "It is not worth the risk, if the result is to effect a cure of ninety per cent in fifteen days, instead of one hundred per cent in two months."

The closed plaster method of treating wounds was described by Ollier in 1870 and was rediscovered in the years from 1914 to 1918. It has been used by the author for twenty years with consistently good results. Immobilization of wounds is complementary to epluchage but does not compensate for inadequate surgical treatment. Immobilization is advocated for large muscular lesions and for wounds of nerves or muscles which may result in malposition. The results of epluchage are better the earlier the procedure is carried out, although many wounds will recover after much delay if the wound is thoroughly opened and any fracture completely immobilized.

The author states: "In the use of sulphonamides we must beware of the exaggerated enthusiasm of certain American writers. This is undoubtedly an excellent auxiliary treatment, but it will never prevent complications without surgical intervention." [ED NOTE (L D B) —A review of the American literature will acquaint the author with the fact that thorough surgical treatment has been recommended by the American surgeons and that a majority of their articles have been written as a warning against any tendency to let the sulfonamide compounds cause them to grow careless.]

Pathologic Fractures —Sirbu and Palmer⁵⁵⁵ report 15 cases of march fracture occurring in the armed forces. It is their opinion that march foot is the result of a definite fracture of the metatarsal occurring in an inherently weak foot. They comment that in all of their cases, and indeed shown in all of the roentgenograms that have appeared in reports of other cases, there has been a short first metatarsal. They conclude that injury occurs from imbalance of the foot that causes undue strain on the second and third metatarsals, which are ill fitted to carry on the unusual stress thrown on them when the person goes into active army training, particularly with addition of a heavy pack. Their fractures were evenly divided between the second and third metatarsals, which again added to their conviction that the condition is due to undue stress on these two metatarsals, caused by faulty distribution of weight bearing, in which the first metatarsal does not carry its share of the weight. The treatment suggested is either immobilization or, as in the majority of their cases, simple strapping of the foot with padding to support the weight away from the involved metatarsal. [ED NOTE —It has been our experience

⁵⁵⁴ Fruchand, H. Treatment of Recent War Wounds. French and Spanish Methods. *Lancet* 1:725-727 (June 20) 1942.

⁵⁵⁵ Sirbu, A. B. and Palmer, A. M. March Fracture. A Report of Fifteen Cases. *California & West Med* 57:123-127 (Aug) 1942.

that almost every patient with march foot required a certain period of rest and fixation in the early convalescent period]

Peterson⁵⁵⁶ states that with the expansion of the Army there has been an increase in march fractures of metatarsals but that spontaneous development of a crack through the lower end of the shaft of the femur has not previously been observed in this country. The findings are typical and resemble those of march fracture in the foot. Treatment is simple, and complete recovery follows adequate immobilization. [ED NOTE—It has come to our attention that Lt Col P M Girard, chief of orthopedic surgery at Brooke General Hospital, Fort Sam Houston, San Antonio, Tex., has observed 3 such cases, which he will report later.]

Epiphyseal Separations—Sloane⁵⁵⁷ reports on a patient 12 years of age who received an injury to the wrist with dorsal displacement of the distal radial epiphysis. Reduction was similar to the treatment of Colles fractures, and a normal wrist resulted. [ED NOTE—The author quotes Aitken's⁵⁵⁸ work in which it is stated that while perfect reduction of the displacement is desirable good results invariably follow even if reduction is not complete. Subperiosteal new bone repairs any defects so that there is no residual disability. The conclusions of one editor (L D B) are that this is not always the case, neither does it warrant neglect or an indifferent attitude toward a diligent attempt at closed reduction with complete replacement of the displaced epiphysis.]

Kaplan, Sprague and Benjamin^{558a} report a case of bilateral traumatic separation of the distal femoral epiphyses without accompanying fracture as a result of extensive injuries to both knees in a child of 11 years. Roentgenograms revealed complete separation of the distal femoral epiphyses with anterior rotation and displacement. With the patient under general anesthesia, traction was applied, and then each leg was forcibly flexed under the thigh while gentle pressure was applied over the epiphysis. Long leg casts were applied with the knees in acute flexion. Roentgenograms revealed perfect reduction. Eight weeks later the casts were discarded and motion begun. Two and a half months later the patient was able to walk without support, and at the end of three and a half months the child had no limitation of motion and walked without a limp. Roentgenograms taken five months after the accident disclosed perfect healing.

External Skeletal Pin Fixation for Fractures—The results obtained in 40 patients treated by the Stader reduction splint by Shaar and Kreuz^{558b} are reported as far more satisfactory than those obtained by any other method previously employed by the authors. The splint is described as being applicable in the treatment of various fractures and in bone grafts, bone lengthening and joint transfixion. The outstanding advantages of this splint, according to the authors, are its structural strength and comparative light weight and its mechanical design, which permits complete control of bone fragments in all planes as well as traction, impaction and fixation. Since the method embodies the basic requirements of accurate reduction, rigid uninterrupted immobilization, immediate active motion and early restoration of function in a single compact unit, it is the most ideal for use aboard ship and in field hospitals and for treatment of a large number of fracture casualties in the shortest period of time. The postoperative care is reduced to a minimum. Joints are free for active motion, and therefore the splint favors earlier union. Insulation of the pins to prevent electrolysis about them is under study. The observations are encouraging, but not yet entirely conclusive. [ED NOTE (L D B)—Many of the patients who have reported to my associates and me in our clinic

556 Peterson, L T. March Fracture of Femur. Report of Case, *J Bone & Joint Surg* **24** 185-188 (Jan) 1942.

557 Sloane, D. Traumatic Displacement of Lower Radial Epiphysis, *Arch Pediat* **59** 594-596 (Sept) 1942.

558 Aitken, A P. The End Results of the Fractured Distal Radial Epiphysis, *J Bone & Joint Surg* **17** 302 (April) 1935.

558a Kaplan, J A., Sprague, S B., and Benjamin, H C. Traumatic Bilateral Separation of the Lower Femoral Epiphyses, *J Bone & Joint Surg* **24** 200-201 (Jan) 1942.

558b Shaar, C M., and Kreuz, F P., Jr. Symposium on New Trends in Surgery Treatment of Fractures and Bone and Joint Surgery with Stader Reduction and Fixation Splint, *S Clin North America* **22** 1537-1583 (Dec) 1942.

for treatment following the use of the various "pin and external splint" appliances have had draining sinuses about the sites of insertions of pins. The study of the insulation of the pins to prevent electrolysis is of interest.

Lewis, Breidenbach and Stader^{558c} present here in detail the construction of and application of the Stader splint, which was first developed for use in dogs. They state that some 1,200 animals have been treated with satisfactory results. The apparatus is one used to connect two half-pins inserted on each fragment of a fracture of a long bone. The principle is similar to that used by Roger-Anderson with his half-pin and external traction splint. The authors present 20 cases, with details on 4. In the 4 cases reported on in detail the results were excellent. They report however, 3 cases of serious infection about the site of the pins which represents some 15 per cent of the cases in which the method was used. [ED NOTE—A 15 per cent incidence of infection seems rather high, considering the many other satisfactory methods which can be used for similar types of fractures. This splint is being given extensive trials at various hospitals, and the final word has not been given as yet. It probably will be found to be highly useful in certain selected cases but hardly applicable for routine treatment for fractures of the long bones. When it is used, it should be by a surgeon who knows how to use it and who knows its limitations.]

Convalescent Care of Patients with Fractures—Kennedy^{558d} makes a timely appeal for proper convalescent care of patients with fractures. He makes many practical suggestions. A patient with a fracture enters the hospital a broken man but not a sick man. It is the doctor's responsibility to keep him from becoming ill. A separate fracture ward is better for morale than placing patients with fractures among those who are ill. It is stimulating to have a set time for daily calisthenics in bed, which keep normal extremities from becoming soft and flabby. A well developed social service department enables the patients to feel that some one really cares how they get along. Occupational work in bed helps overcome the tendency to give up and leave it all to the compensation board. [ED NOTE—These high lights give only a rough outline of the intelligent approach made by the author to the problem of preserving patients' morale.]

B FRACTURES OF THE NECK OF THE FEMUR

Hart⁵⁵⁹ in reporting 2 cases of fracture of the femoral neck emphasizes the importance of the difference between the adduction type of fractured neck of the femur, in which there are a separation of the fragments and a shearing force across the line of fracture that tend to keep the fragments apart and prevent union, and the abduction type, in which the fracture is impacted and the head is thrown into valgus position on the neck and fortunately either weight bearing or muscular pull forces the fragments together rather than apart. With the first type of fracture it is important to get adequate fixation, preferably internal fixation, in order to secure union. The second type of fracture is already impacted and in excellent position. This type of fracture always unites without any special form of treatment, the author states. [ED NOTE—The author's last statement should be modified as follows: "In most instances an impacted valgus fracture of the femoral neck unites"]

Compere, Wallace and Lee⁵⁶⁰ discuss various materials for internal fixation of intracapsular fractures of the neck of the femur. Hips obtained at necropsy

558c Lewis, K. M., Breidenbach, L., and Stader, O. The Stader Reduction Splint for Treating Fractures of the Shafts of the Long Bones, *Ann Surg* **116** 623-636 (Oct) 1942

558d Kennedy, R. H. Convalescent Care of Patients with Fractures *Am J Surg* **55** 309-316 (Feb) 1942

559 Hart, V. L. Fractures of the Neck of the Femur, *Surgery* **12** 763-767 (Nov) 1942

560 Compere, E. L., Wallace, G., and Lee, J. Materials for Internal Fixation of Intracapsular Fracture of Neck of Femur, *Arch Surg* **44** 327-338 (Feb) 1942

were freed of all soft tissue with a minimal amount of trauma to the periosteum, but no dissolving, decalcifying or fixing chemicals were used. Each femur was mounted in a plaster of paris cylinder which extended just above the lesser trochanter. A concave plaster mold was made to fit over the femoral head, so that force could be directed downward on the head over a wide area by means of a hydraulic press. All hips were fractured with a measured force, and most fractures of the neck occurred from the superior edge of the head downward and laterally toward the lesser trochanter. The average force of fracture in a group of 13 hips was 1,655 pounds (745 Kg), in a group of 5 the force was 1,769 pounds (796 Kg), and in a group of 4 it was 1,456 pounds (655 Kg). After almost anatomic reduction, insertion of three highly tempered stainless steel wires, gage 0080, with fifty-six threads to the inch, the breakdown or refracture force averaged 455 pounds (205 Kg) for the first group, of 13 hips. In the second group, of 5 hips, three Steinman pins were introduced, and the breakdown force averaged 372 pounds (167.5 Kg). In each of the remaining 4 hips a Smith-Petersen nail was introduced, and the average refracture force was 348 pounds (156.5 Kg). The threaded wires compared favorably with the larger nail or pins in resisting breakdown force. Holding or distraction force was also measured by calculating the force in pounds required for pulling the head and neck apart at the line of fracture after pinning with the Smith-Petersen nail, three Steinman pins or three threaded wires inserted in the usual criss-cross fashion. This distraction force averaged 50, 87 and 116 pounds respectively (22.5, 39 and 52 Kg). The authors found the average breakdown force of hips pinned with wires in the transverse position to be 726.6 pounds (327 Kg), as compared with that of the contralateral hips pinned with obliquely placed wires, which was 452 pounds (203.5 Kg)—a difference of 271 pounds (122 Kg).

The authors concluded that the holding power of three small threaded steel wires is greater than that of the Smith-Petersen nail or of larger nonthreaded Steinman pins. Small threaded nuts on each wire may be tightened securely against the lateral cortex of the femur to prevent migration. The authors felt that the insertion of threaded steel wires produced minimal trauma to cancellous bone and were unlikely to injure nutrient blood vessels since they constitute no real obstruction to revascularization. They have used this method successfully both in the treatment of recent fractures of the neck of the femur without casts and with almost immediate ambulation and also in conjunction with tibial bone grafts in the treatment of old ununited fractures of the neck of the femur, and they did not find it necessary for immobilization. They state that this method is mechanically efficient because it is believed to be physiologic, relatively atraumatic and less likely to contribute to delayed aseptic necrosis than methods requiring grosser trauma and greater displacement of cancellous bone of the fractured fragment.

Thomas⁵⁶¹ discusses the end results of screw fixation in the treatment of intracapsular fractures of the femoral neck. After reduction he used Whitmann's abduction-internal rotation cast and operated through a window overlying the greater trochanter. He states that after incision a finger may be pushed anterior to the trochanter to determine the direction of the neck and a carpenter's screw may be introduced $\frac{1}{2}$ inch (1.27 cm) below the margin of the trochanter. The second screw may be introduced just below the first far enough so as not to overlap the head of the upper screw. The patient remained in the cast for ten days and generally had a satisfactory result. No infections occurred, and there was only 1 instance of nonunion, which was due to the screws' being too long. After removal of the two screws and the introduction of a third screw, this patient still had nonunion with aseptic necrosis. One patient because of a second fall had a refracture through the screws, but after introduction of another screw union occurred. The author states that satisfactory results may be obtained by this method.

⁵⁶¹ Thomas, T. T. End Results of Screw Fixation in Intracapsular Fractures of Neck of Femur, *Am J Surg* 57:65-75 (July) 1942.

Fitzgerald and Clark⁵⁶² describe a combined film holder and pelvic rest which helps achieve accurate, rapid and clear roentgenograms during operations for fractures of the femoral neck. The apparatus holds the film steadily or at the correct angle and in the same position for each exposure. The x-ray film may be removed from the opposite side of the table from the operator. [ED NOTE—The apparatus appears to be simple and practical.]

Cleveland⁵⁶³ reviews 110 fractures of the femoral neck treated during a decade extending from 1930 to 1940. The first 50 patients were treated by manipulation and application of a plaster of paris spica or traction in a few instances. Fourteen per cent of these patients died as a result of the fracture, and 61 per cent had nonunion. In 1935 internal fixation was first used with open reduction, and of the 14 patients treated in this fashion only 7 or 50 per cent obtained union, and in only 2 of these was the result wholly satisfactory.

In the second group, of 60 patients, 52 were treated by open reduction and 8, who had undisplaced fractures, were not operated on. The 8 who were not operated on all had healing without evidence of condensing osteitis of the femoral head or aseptic necrosis. The three phalange nail was used in all cases in which operation was performed. In 3 of the cases nonunion and extensive aseptic necrosis developed, and in 2 there was bad nonunion with pronounced deformity. In some cases of open reduction there developed overgrowths from the acetabular margins, perhaps due to stripping of the periosteum. Closed reduction and internal fixation were carried out for 37 patients, in 27, or 73 per cent, union resulted, but 4 had slight condensing osteitis and 1 advanced aseptic necrosis. Twenty-five, or 86 per cent, of this group are living and have union. Cleveland states that adequate reduction and internal fixation result in a high percentage of union. Of the 38 patients treated by closed reduction and internal fixation, 26, or 68 per cent, had almost perfect reduction, and in 6, or 16 per cent, the fracture was reduced so that bony apposition was 75 per cent or better. In 5 there was malunion, with resulting deformity. In 2 of the cases of malunion there were circulatory changes in the femoral head. Cleveland states that the most important cause of such circulatory disturbance has been failure to reduce the fracture and keep it reduced. He also points out that actual or so-called migration of the nail is usually due to improper reduction and that migration occurs almost exclusively in ununited fractures. Patients with nonunion may be benefited by a trochanteric osteotomy. In his series accurate reduction of a fractured neck of the femur by manipulation and fixation by a properly placed three phalange nail resulted in unions in a high percentage of patients, and 86 per cent survived with only a low incidence of circulatory disturbance in the femoral head. [ED NOTE—This is an excellent review of an important subject.]

Brittain⁵⁶⁴ describes internal fixation with a three phalange nail for treatment of trochanteric or extracapsular fractures of the femur. He mentions that treatment of trochanteric or basal fractures of the neck by traction on a Thomas splint or by a plaster of paris spica is extremely difficult and requires skilled nursing and constant attention of the surgeon. The disadvantages of nailing this type of fracture are presented. The operation is difficult because the cortical bone splinters into the fracture, it is a more formidable operation than the medial nailing requiring a more extensive exposure, and the fracture generally unites in any event. His operative technic and after-treatment are described. He states that splintering can be controlled by making a furrow with a gage extending $1\frac{1}{2}$ inches (3.8 cm) downward from the trochanteric edge and just wide enough to admit the phalanges of the nail and not the head. Fractures of the shaft below the site of insertion of the nail occurred in 2 patients as a result of a fall but subsequently united uneventfully. He states that rotation deformity cannot occur

562 Fitzgerald, F. P., and Clark, K. C. Radiography of Femoral Neck, *Lancet* 2 183-184 (Aug 15) 1942.

563 Cleveland, M. A Critical Survey of Ten Years' Experience with Fractures of the Neck of the Femur, *Surg, Gynec & Obst* 74 529-540 (Feb, no 2A) 1942.

564 Brittain, H. A. Low Nail, *Brit M J* 1 463-464 (April 11) 1942.

because of the position of the nail but that adduction deformity occurred in 3 patients, explained on the basis that the nail was not long enough. He states that a hold of 2 inches (5 cm) in the upper fragment and 2 inches in the lower should be enough to hold the fragments. During the two years prior to July 1941, between 40 and 50 patients had trochanteric fractures nailed, with good results in over 75 per cent of the cases.

Plummer and Potts⁵⁶⁵ discuss end result of the treatment of approximately 125 fractured hips by means of internal fixation. Kirschner wires were first used but were found to be unsatisfactory. Moore pins were used with satisfaction, but in the last few years three phalange nails were used. All fractures of the femoral neck were treated by manipulation and internal fixation irrespective of the patient's age or the presence of a complicating lesion. The authors state that the more simple, impacted transcervical fracture is just as much entitled to this form of treatment as the fractured neck with marked separation of the fragments. Difficulty of reduction, inability to maintain the reduction and failure of the nail to get a firm grip in the proximal portion of the neck and head were thought to be due to obliquity of the line of fracture. The authors felt that this constituted one cause of failure. If a valgus position was obtained, slight unreduced rotation was not changed, and it was not believed to be a factor in the unfavorable results. The authors felt that a 75 per cent approximation of the neck to the head would allow for adequate placing of the nail and would give a satisfactory result. They also felt that impaction was not logical or practical and that internal rotation produced sufficient impaction without further damage to the blood supply. One difficulty encountered was protrusion of the nail through the upper part of the head, which occurred when the position of the nail in the head was high. They felt that the best position for the nail was in the center of the head or slightly below, with the arm of the Y toward the upper portion of the head. Some patients experienced pain at the end of ten days. In their cases roentgen examination showed the nail backed out or the head disengaged from the nail. It was felt that this occurred when the fracture line was oblique or the fracture was comminuted. Aseptic necrosis of the femoral head occurred in a case in which the fracture was easily reduced and the reduction was maintained. Two patients had nonunion without aseptic necrosis, and after open reduction with the removal of scar tissue at the fracture line satisfactory results were obtained. Two failures were reported with this same procedure where the heads were necrotic. The authors have also noted that after satisfactory reduction and nailing protrusion of the nail and definite changes in the relations of the head and neck were present a year later. Here, they point out, the interpretation of satisfactory union made roentgenographically was incorrect. They allowed the patients to bear weight only after trabeculations could be seen across the fracture line. The authors feel that failures are due in part to the operators and in part to circulatory changes occurring at the time of fracture.

West⁵⁶⁶ discusses the treatment of slipped upper femoral epiphyses and divides the patients treated into five general groups. The patients in whom the deformity is so slight that reduction is not necessary were treated by simple fixation and protection, either by plaster or by the Thomas caliper walking splint. The patients in whom the injury was of recent origin and the deformity mild were treated by manipulation under anesthesia. It was felt that this could be carried out without damage to the femoral head. The patients in whom the deformity was further advanced and union was more definite were treated by simple osteotomy with a large wood carver's chisel through the epiphysal line, followed by proper protection. The author states that for the patients in whom the union was solid and the neck showed a typical torsion as the result of malunion the best treatment was by osteotomy and proper maintenance of position. Some of these patients

⁵⁶⁵ Plummer, W. W., and Potts, F. N. Some End Results of Internal Fixation of Hip, *New York State J. Med.* **42**: 997-999 (May 15) 1942.

⁵⁶⁶ West, W. K. The Treatment of Slipped Upper Femoral Epiphyses, *South. M. J.* **35**: 1082-1085 (Dec.) 1942.

were treated by manipulative reduction and the insertion of a three phalange nail. The author points out the difficulty of proper placement of the nail in a child and the danger of the nail's penetrating the hip joint proper. For the fifth group of patients, in whom the deformity was severe, union solid, the head widened and the neck thickened, subtrochanteric osteotomy was carried out for correction of the rotation and improvement of the coxa vara, which resulted in an increased range of abduction. There were 42 cases in the author's series, who were treated over a period of eleven years. He points out that skeletal traction prior to open reduction may prove beneficial. He states that when even expert orthopedic surgeons use the Smith-Petersen nail there is danger of damage to the necrotic head. He believes that an arthroplastic procedure should be done rarely, because of shortening the leg, instability and the possibility of a permanently painful hip. Ten case reports are given in detail.

If the Smith-Petersen nail and similar devices are to be placed on a surer basis, Bankart⁵⁶⁷ indicates some points which seem to call for further consideration. He discusses the selection of cases and points out several feasible contraindications for nailing. He feels that in some instances it is better to do a transtrochanteric osteotomy at once rather than to wait for failure of a nailing operation. He recalls that the impacted subcapital abduction fracture always heals with bony union if it is treated in a short plaster spica that permits the patient to walk, he suggests that weight bearing on an impacted fracture is not in itself harmful so long as the joint is not moved, and he considers whether this has any bearing on the treatment of adduction fractures after internal fixation and questions whether in fact the nailed adduction fracture should not be treated in the same way as the impacted abduction fracture, in a short, ambulatory plaster spica. When fractures unsuitable for nailing have been eliminated, the principal causes of failure are imperfect reduction of the fracture, faulty application of the nail and inappropriate after-care. For reducing the fracture he feels that well leg traction is the best method, as the device can be adjusted at leisure and when the reduction is perfect the patient can be lifted safely onto the operating table with the traction apparatus still on the limb. In inserting the nail, he points out that the more vertically the nail is placed the less will be the breaking strain across it and the more will the proximal fragment be guided toward and pressed against the distal fragment by pressure from above. He states that the best angle for the nailing is one of 140 degrees with the long axis of the shaft of the femur. He points out that it must be remembered that a nail can hold fragments apart as well as hold them together. He feels that the common practice of forbidding weight bearing for some months after the operation while encouraging active movement of the hip should be reconsidered, and he gives reasons for believing that early weight bearing should be encouraged while movement of the hip should be prevented until bony union has taken place. He outlines his technic for the nailing operation and points out the importance of anchoring the proximal fragment to the pelvis while the nail is being driven in, in order to avoid displacement of the head by the oncoming nail. [ED. NOTE—The article is timely and contains many excellent suggestions.]

Cochrane⁵⁶⁸ refers to the recent developments in the treatment of fractures of the femoral neck and to the fundamentals of their management. He reviews statistics on results of the treatment of such fractures by external fixation through the medium of the plaster hip spica and by internal fixation with the Smith-Petersen nail, finding the incidence of nonunion, 12 per cent to 15 per cent, to be approximately the same by both methods in the series cited. He does not advocate the use of the plaster fixation method routinely. He notes the points to be considered in selecting cases for its employment, such as the exact site of the fracture in the neck, the mechanism of its production, the resultant "fracture-shaft angle,"

⁵⁶⁷ Bankart, A. S. B. Treatment of Intracapsular Fractures of Femoral Neck, *Lancet* 1: 249-252 (Feb. 28) 1942.

⁵⁶⁸ Cochrane, W. A. Flexed Plaster Spica for Fractured Femoral Neck, *Lancet* 2: 726-728 (Dec. 13) 1941.

the time interval since injury and the facilities available for internal fixation. The main differences between the author's method and that of Whitman, advocated forty years ago, are (1) roentgenograms taken in two planes, to prove reduction, the great importance of which he emphasizes, (2) immobilization of the hip in flexion of from 50 to 60 degrees, rather than in extension, and in relatively less abduction, about 20 degrees from the midline, (3) careful application of the spica, to attain lightness and close fit.

Dudgeon⁵⁶⁹ reports a treatment of fracture-dislocations about the pelvis that consists in (1) application of full length leg plasters, (2) incorporation of turnbuckles into the medial aspects of the leg plasters at the proximal level and the ankle level and (3) correction of pelvic displacements by manipulation of turnbuckles.

The results of treatment of 2 patients are reported. One, with compression of the pelvis and protrusion of the femoral head through the acetabulum, obtained excellent reposition, while the other, with wide separation of the symphysis and dislocation of the sacro-iliac joint, obtained a reduction of the symphysis but no improvement of the sacroiliac dislocation.

Funsten, Frankel and Harris⁵⁷⁰ report 2 cases of unusual traumatic dislocation of the hip. The first is the case of a 49 year old man with upward displacement of a fragment from the superior rim of the acetabulum and the femoral head, in whom the fragment eventually formed a solid shelf which allowed full weight bearing eleven weeks after injury. The hip was stable and painless and exhibited an excellent range of motion. The second case is that of a 24 year old Negro in whom an axe wound of the hip, incurred twenty hours before his admission to the hospital, resulted in a fracture of the greater trochanter with displacement, laceration into the femoral head and lateral anterior and superior dislocation. Immediate debridement, reduction, fixation of the trochanter with wire, closure with drains and local implantation of a sulfonamide compound were done. Healing was by first intention, motion was started nine weeks later, and full weight bearing was permitted eighteen weeks after the reduction. Examination twenty-five weeks after the patient's injury showed no limp and a painless hip with good motion except in flexion, which was limited to 50 degrees. The danger of closing this wound twenty hours old was weighed against the adverse effect of leaving the joint open. The authors plan to wait for longer follow-ups before evaluating end results.

Hart⁵⁷¹ reports a case of severe fracture-dislocation of the hip in a 46 year old man, associated with a compound fracture of the patella in the same extremity. The latter condition was treated immediately by the usual methods, with excision of the entire fragmented patella. Primary closure was done and healing was obtained without infection. One month later the hip was treated by the method advocated by Watson-Jones, excision of the loose and displaced femoral head, followed by a Whitman reconstruction, the neck of the femur being placed in the joint. Plaster immobilization was employed, with the extremity maintained in the position of election. The convalescence was uneventful. Ankylosis of the hip in good functional position resulted.

Romney,⁵⁷² after a critical survey of the various operations devised for fracture of the neck of the femur, enumerates the advantages of the Godoy Moreira method. (1) The screw has a helicoid thread resembling the Danis screw but is deeper and sharper, so that an excellent hold on the femoral head is afforded, (2) tests showed that this nail required 251 Kg to bend it and 317 Kg to rupture it, pressures two or three times those tolerated by nails and pins of other types,

⁵⁶⁹ Dudgeon, H., Jr. Pelvic Fractures and Dislocations Reduced by Turnbuckles, *J. Bone & Joint Surg.* **24** 354-358 (April) 1942.

⁵⁷⁰ Funsten, R. V., Frankel, C. J., and Harris, L. Two Unusual Traumatic Dislocations of Hip, *J. Bone & Joint Surg.* **24** 443-446 (April) 1942.

⁵⁷¹ Hart, V. L. Fracture-Dislocation of Hip, *J. Bone & Joint Surg.* **24** 458-460 (April) 1942.

⁵⁷² Romney, H. Treatment of Fractures of Neck of Femur Using the Technique of Godoy-Moreira, *Rev. de med. y cir., Habana* **46** 547-571 (Dec. 31) 1941.

(3) it is not necessary to use a hammer to insert the screw, (4) the screw will not slip inward or outward, (5) the firm hold prevents trophic disturbances due to malnutrition, (6) the solidity obtained is superior to that of the normal femoral neck and permits early ambulation without crutches or other support (walking was possible between the seventh and the twelfth day in the author's cases) [ED NOTE—The Godoy Moreira technic is described by Godoy Moreira himself in an article in the *Journal of Bone and Joint Surgery*] ⁵⁷³

Sosa ⁵⁷⁴ presents a new type of graft-bearing nail for use in the treatment of transcervical and subcapital fractures of the neck of the femur. This graft, in his opinion, solves the biologic problems of repair of fractures. The nail has four phalanges for the cephalic fragment, a middle portion, also with four phalanges, which is narrower, for incrustation with the graft, and an outer portion, a threaded pin to receive the head to be screwed thereon, to fasten in the cortex of the trochanter. The bone graft is cut the same length as the middle portion of the nail and drilled. The nail is introduced into it and the head screwed on and fixed with a wedge, when everything is ready for nailing. [ED NOTE—One editor (L. D. B.) does not consider this the final achievement and believes that better means of fixation will be developed for fractures of the femoral neck.]

Hoffheinz ⁵⁷⁵ reports a series of 161 cases of nailed fractures of the femoral neck. He discusses indications, preoperative treatment and operative technic. In this series the mortality rate was 9.9 per cent, as compared with 14.6 per cent in the author's earlier series. He does not believe that nailing is indicated for young subjects, in whom healing usually takes place. However, if conservative measures fail, nailing may be tried. The average age of the patients whose fractures were nailed was 68 years, and the oldest patient was 92.

In fractures of the trochanter, the trochanter is so involved that there is not sufficient solid bone to hold the nail. As a rule the author waits for eleven days after the accident before operating. The use of two roentgen apparatus is preferable, facilitates operation, increases asepsis and also precludes confusion from incorrect projection of the bundle of rays. The guide wire must be strong enough not to bend and should almost fill the nail canal. The failure to accomplish exact reduction does not necessarily mean an unsuccessful operation. The author disapproves of guiding instruments. The nail must be driven in until the head lies well within the cortical layer. The length of the nail is chosen so that the tip of the nail lies 1 cm. from the cartilage covering of the head. Since the author has closed the nail canal surrounding the wound in the bone with wax, the number of postoperative hematomas has diminished considerably.

After nailing necrosis usually does not develop until after a period of years of respite, whereas after conservative treatment if necrosis does develop it usually occurs much earlier and the patient never walks again. The few years of respite are valued by these old people.

XX FRACTURE DEFORMITIES

PREPARED BY J. SPENCER SPEED, M.D., MEMPHIS, TENN.

Hermann, Reineke and Caldwell ⁵⁷⁶ supplement previous reports by Hermann and Caldwell in an article in which they reaffirm and elaborate on their previously expressed ideas regarding the causation, roentgenologic characteristics and treat-

⁵⁷³ Godoy Moreira, F. E. Special Stud-Bolt Screw for Fixation of Fractures of Neck of Femur, *J. Bone & Joint Surg.* **22** 683-697 (July) 1940.

⁵⁷⁴ Sosa, U. Graft-Carrying Transcervical and Subcapital Fractures, *Cir. ortop. y traumatol., Habana* **9** 88-97 (April-June) 1941.

⁵⁷⁵ Hoffheinz, S. Fractures of Neck of Femur. Modern Therapy, Critical Study, *Arch. f. klin. Chir.* **201** 584-596, 1941.

⁵⁷⁶ Hermann, L. G., Reineke, H. G., and Caldwell, J. A. Post-Traumatic Painful Osteoporosis. Clinical and Roentgenological Entity, *Am. J. Roentgenol.* **47** 353-361 (March) 1942.

ment of post-traumatic painful osteoporosis. The authors prefer this term rather than acute osseous atrophy, as they feel that it more nearly portrays the clinical and pathologic character of this disease entity, which is manifest as a patchy demineralization of bone associated with coexisting signs of vasomotor instability, trophic changes in the soft tissues and pain. Disturbance in function is always greater than is to be expected from the trauma alone.

Three types are differentiated: (1) osteoporosis following minor trauma about one of the polyarticular regions, such as the wrist or the foot, (2) osteoporosis following trauma sufficient to produce fracture, usually about a joint, and (3) osteoporosis associated with minor traumatic disturbances in which tendons or periarticular structures appear to be first involved, with the typical changes in the bone.

Early adequate treatment is insisted on by the authors if severe and prolonged disability is to be avoided. They do not feel that any of the conservative methods of treatment commonly used, such as immobilization, various forms of physical therapy or active use, materially affects the course of the disease. Roentgen therapy, as recommended by Mumford, reduces the pain, but in 18 patients on whom the authors tried it they found that the destruction of bone continued and the disturbance in function was unaltered. Removal of or making injections into the sympathetic ganglions is not successful, because the disease is produced by disturbed function in the neurotrophic fibers lying in the adventitia of the major artery supplying the part, and these fibers do not pass through the sympathetic ganglions. Periartrial sympathectomy, suggested by Heyman, has given the only reliable results in the authors' opinion. They report 34 cases of periartrial sympathectomy with excellent results and recommend this as the treatment of choice.

Miller and de Takats,⁵⁷⁷ after an exhaustive review of the various anatomic and physiologic factors relating to post-traumatic dystrophy (painful osteoporosis) offer certain explanations regarding the causation and suggestions as to the treatment which are at considerable variance with those expressed in the preceding article.

They conclude that careful examination in the early stages of post-traumatic dystrophy will reveal a source of continuous nerve stimuli which are responsible for the sensory and vasomotor phenomena. The evidence regarding the origin of these painful stimuli is at present controversial and somewhat contradictory. The vasomotor dilatation with increased blood flow through the extremity is a well recognized phenomenon in the early stages of traumatic osteoporosis. Sympathetic block, which also produces vasodilatation, definitely relieves the pain and produces clinical improvement. This apparent contradiction may be explained by an incomplete understanding of the transmission of pain impulses through the sympathetic nervous system.

Whatever the explanation, prevention of pain by complete fixation of injuries with repeated sympathetic block in the earlier stages and sympathectomy in the more intractable cases has been of decided benefit.

[ED NOTE—While there can be no argument that post-traumatic painful osteoporosis always produces severe and prolonged disability and sometimes permanent deformities and loss of function, it is equally true that most of the patients recover with, or in spite of, some form of conservative treatment. It is not always possible in the early stages of the disease to determine whether or not it is going to be of the intractable type. Neither periartrial sympathectomy nor sympathetic ganglionectomy is a minor surgical procedure, and the ultimate effects of these operations are not thoroughly understood. Since authors who have admittedly given this subject as intensive study as any authority differ so widely in their published opinions regarding the results of treatment, it does not appear that such radical measures are yet justified by the evidence presented.]

⁵⁷⁷ Miller, D. S., and de Takats, G. Post-Traumatic Dystrophy of Extremities. Sudeck's Atrophy, Surg., Gynec. & Obst. 75: 558-582 (Nov.) 1942.

Clinical observation has added little in recent years to the knowledge of formation of callus and healing of fractures. One expectantly looks to the field of biochemistry for future help in explaining this commonplace yet still obscure physiologic process. The apparent paucity of practical results gained from this field of experimental medicine has not discouraged those interested in the subject, and each year the results of new work published add positive or negative facts to the gradually accumulating data.

Armstrong, Sperling and Litow⁵⁷⁸ report the results of the use of sodium betaglycerophosphate in connection with the healing of experimental fracture in rabbits. Although the phosphatase activity of a fracture callus increases rapidly during the first few days after the injury, there is no evidence that defective calcification or delay in healing of a fracture is primarily a result of a quantitative deficiency of this enzyme.

While the erythrocytes are high in phosphoric esters hydrolyzable by phosphatase, the blood plasma is relatively low. The authors felt that one of the factors limiting the speed of the calcification process might be the low content of plasma with respect to the substrate of bone phosphatase, and this consideration suggested that some instances of delayed union or nonunion of fractures might be so explained.

Twenty-seven rabbits with experimental fractures received six to fourteen daily intravenous injections of 0.1 Gm. of sodium betaglycerophosphate. All the animals were killed the day after the last injection. Examination of the sites of fracture grossly and by roentgenograms revealed a larger amount of callus in the animals that had received injections than in the control group. The observations indicated that in the majority of cases the drug exerted a positive effect in increasing the rapidity and amount of callus formation. Four determinations of inorganic phosphate and calcium in the serum made at regular intervals during the course of twelve daily injections showed no consistent differences from values in the untreated animals.

Since sodium betaglycerophosphate is harmless in a wide range of dosage, it should be safe to administer it to human beings in order to determine its effect on those fractures which heal at a rate slower than usual.

Rhoads and Kasinkas⁵⁷⁹ investigated the effect of hypoproteinemia on the formation of callus in experimental fractures. Hypoproteinemia has been shown to retard the healing of wounds of soft tissues in experimental animals. The authors' study was made to determine if it might also exert an adverse influence on the healing of fractures.

In a small series of dogs hypoproteinemia was produced by a low protein diet and by repeated plasmaphoresis. Experimental fractures in this group of dogs showed a consistent delay in healing as compared with the control series.

The rationale back of their experiment was based on the accepted fact that a large portion of the serum calcium is bound to the serum protein, so that when serum protein is low serum calcium is also reduced. Sufficient clinical data are not available to warrant the assumption that hypoproteinemia is a factor in delayed union or nonunion of fractures in human beings.

In spite of the extensive clinical experience indicative that sulfonamide compounds do not interfere with the healing of wounds in soft tissues or exert any inhibiting action on callus formation, there is still considerable opposition by many surgeons to the local implantation of those drugs in wounds. Some of this opposition is probably based on such experimental work as that of Veal and Klepser,⁵⁸⁰

578 Armstrong, W. D., Sperling, L., and Litow, S. Effect of Phosphoric Acid Esters on Fracture Healing, *Proc. Soc. Exper. Biol. & Med.* **49** 169-171 (Feb.) 1942.

579 Rhoads, J. E., and Kasinkas, W. Influence of Hypoproteinemia on Formation of Callus in Experimental Fracture, *Surgery* **11** 38-44 (Jan.) 1942.

580 Klepser, R. G. Problems in the Local Use of Sulfonamides, *M. Ann. District of Columbia* **11** 211-213 (June) 1942.

who noted a deleterious effect of powdered sulfonamide compounds on normal cellular activity, and on pathologic studies on rats by Davis, Harris and Schmeisser,⁵⁸¹ who observed a nonspecific foreign body reaction to crystalline sulfonamide compounds

Horwitz⁵⁸² reviews the literature pertaining to the controversy and adds both experimental and clinical data to prove that sulfonamide compounds in powder form have no adverse effect on healing of bone or on the fate of transplanted bone. In experiments with adult rabbits bone grafts were transplanted from the iliac crests to the tibia and from one tibia to the other. Sulfanilamide or sulfathiazole crystals were implanted in the wounds of one group, and for a similar control group no drug was used. The bones operated on were removed at intervals of one to eight weeks for roentgenologic and microscopic study. Grossly and roentgenologically the transplanted grafts were solidly united to the host bone in four weeks, there being no demonstrable difference between the treated and the control group. Microscopically the grafts in both groups passed through the usual stages of necrosis and vascular resorptive substitution with fibrous tissue in which new bone was formed. The only difference noted in the two groups was that in the wounds in which the sulfonamide drugs were implanted the fibroblastic reaction of the paraosseous tissues appeared excessive. In 5 clinical cases in which grafts were transplanted into infected or potentially infected areas in conjunction with local implantation of a sulfonamide compound the wounds healed by first intention and progress of the graft in the various procedures of union appeared normal.

[ED NOTE—Clinical experience of one editor (J. S. S.) and of hosts of other surgeons in many hundreds of cases amply substantiates the conclusions just cited. Local implantation of sulfonamide compounds in operative wounds does not produce any undesirable reaction, and its bacteriostatic action permits a much bolder and earlier surgical solution of many infected or potentially infected non-unions. Flare-ups of low grade infections still occur after such operations, but it is extremely rare to see the severe fulminating recurrences of infection with sloughing of the soft tissues and sequestration and loss of the graft which used to be seen. Sterilization of the drug is apparently unnecessary.]

Some interesting ideas regarding the behavior and fate of transplanted cartilage and bone are given by Mowlem⁵⁸³ in reviewing a series of such grafts utilized chiefly in repairing defects of the ear and nose. Transplanted costal cartilage, which is a relatively avascular structure, does not undergo absorption even after a period of years. Grossly the graft changes little in size or shape, there being only slight evidence of cellular growth, although microscopically the cellular structure of the transplant appears relatively normal. Mowlem states that there is a wealth of literature on the subject of survival of bone, and a corresponding great diversity of opinion. After reviewing the various theories, the author concludes that with the exception of that of Leriche and Policard, the conflicting ideas may not be wholly irreconcilable. It seems probable that the bone cells in a transplant have the power of survival but that this is dependent on the rapidity with which they can acquire nutriment in their new position. The nutriment will, as in the case of other grafted tissue, first be derived from blood serum and tissue fluid and only later be supplied by the ingrowth of any real vascular supply. The structure of the bone determines to a great extent the accessibility of the enclosed cellular element to this nourishment. This will vary considerably between dense cortical tibial grafts and a piece of cancellous ilium.

Mowlem stresses two other points which appear to bear out the suggestion that an early and adequate nutritional supply is essential to the actual survival

581 Davis, H. A., Harris, L. C., and Schmeisser, H. C. The Toxic Effect of Sulfanilamide Upon Tissues of Rats, *J. Lab. & Clin. Med.* 25:1263-1275 (Sept.) 1940.

582 Horwitz, T. Effect of Sulfanilamide Crystals, Used Topically on Fate of Transplanted Bone. Some Experimental and Clinical Observations, *Surgery* 11:690-697 (May) 1942.

583 Mowlem, R. Bone and Cartilage Transplants. Their Use and Behavior, *Brit. J. Surg.* 29:182-193 (Oct.) 1941.

of the graft. If cancellous iliac bone is placed in the fatty tissues of the abdominal wall it will rapidly atrophy, but if placed in the vascular tissues of the face it may hypertrophy and form a new cortical covering of normal cortical architecture. The second point is that epiphyseal bone and epiphyseal cartilage show considerably more tendency to be absorbed than more mature structures. One assumes that this is due to the fact that the bone cells, being younger and more active, have a higher metabolic rate and therefore do not survive even the short transitional period during which their nutrition is absent.

Further data in reference to regeneration of bone and the viability and regeneration of partial or complete joint transplants are contained in an article by May⁵⁸⁴. He summarizes his own experimental and clinical conclusions and the experience of others as follows: Transplantation of whole joints with their capsules, either homogenous or autogenous, has been discouraged, particularly in weight-bearing joints, because of degeneration or ankylosis due to incomplete revascularization and resultant necrosis. Homogenous hemitransplants have proved unsatisfactory for the same reasons. Autogenous hemitransplants have proved to be relatively good, particularly smaller bones, such as the fibula for replacing the upper end of the humerus or the lower end of the radius. In these the bone undergoes a primary necrosis, just as occurs in bone grafts with later regeneration, by a process of substitution and new bone formation. The outer layers of the articular cartilage remain viable, and the deeper layers undergo partial necrosis, but all these cartilage cells later become completely viable if the bone is revascularized within a year's time. The author reviews the present data regarding the revascularization and regeneration of the articular fragment in such fractures as intra-capsular fractures of the femoral neck and carpal scaphoid and points out the biologic similarity of the healing of such fractures to that following hemitransplantation of joints.

Transplantation of portions of a bone containing an active epiphysis universally results in cessation of epiphyseal growth. [ED NOTE—Transplantation of the fibula, including its upper articulation, has been employed successfully for many years in non-weight bearing joints. It has not been satisfactory in replacing the external malleolus in congenital absence of the lower end of the fibula, probably because the operation is necessarily done at an age when the epiphysis is still active and because it forms part of a weight-bearing joint. This same principle accounts for the unsatisfactory results in the correction of malunions in which it is necessary to mobilize completely joint fragments containing actively growing epiphyses, such as malunited fractures of the humeral condyles in children. Mowlem's observation, previously cited, that neither young epiphyseal bone nor actively growing cells at the epiphyseal plate could withstand even temporary loss of nutriment through interruption of their blood supply is fully corroborated by clinical experience.]

Milch⁵⁸⁵ reports the use of a fibular graft replacing the lower end of the radius after resection for a giant cell tumor. The lower end of the fibular transplant was fixed to the carpal scaphoid by arthrodesis, and a cuff resection of the lower portion of the ulna was done to permit rotation of the forearm. The functional result was good except for loss of motion of the wrist. [ED NOTE—A somewhat similar operation has been successfully employed by one of the editors (J. S. S.) in 4 cases of giant cell tumor of the lower end of the radius, in which both motion and stability of the wrist joint were retained. The upper articulation of the fibula with the tibia closely resembles in shape the lower articulation of the radius. It is also covered with hyaline cartilage. A sufficient length of the upper end of the fibula with its articulation is resected and transplanted to replace the resected portion of the radius, the previous tibiofibular articulation forming the new radio-

584 May, H. Regeneration of Joint Transplants and Intracapsular Fragments, *Ann Surg* 116 297-310 (Aug) 1942

585 Milch, H. Forearm Reconstruction Following Partial Resection of Radius, *Bull Hosp Joint Dis* 3 100-104 (July) 1942

carpal joint Possible degeneration of the articular cartilage with a resultant painful arthritis has not been reported observed by others or noted in personal observation in 1 case as long as four years]

Rothberg⁵⁸⁶ emphasizes the importance of greater diagnostic care when a fresh fracture of the carpal scaphoid is suspected The clinical signs and symptoms should receive more emphasis and the roentgenographic less An initial roentgenogram with no evidence of a fracture does not necessarily rule out the possibility of one Several variations from the usual technic may be employed when the ordinary anteroposterior and lateral views fail to reveal a fracture Views should be taken with the hand in ulnar deviation and with two exposures, the one with a tube shift a little to the right and the other to the left In some cases in which a fracture line cannot be demonstrated at the time of the initial fracture, roentgenograms taken weeks later may reveal the site of fracture, brought to light by the process of osteoporosis

In a second article, discussing the treatment of ununited fractures of the carpal scaphoid, Rothberg⁵⁸⁷ recommends simple drilling followed by ten weeks of immobilization in a cast He states that this method is not applicable in all cases and enumerates other procedures, such as removal of all or part of the scaphoid, resection of the entire proximal row of carpals and fusion of the wrist, as sometimes necessary [ED NOTE—The whole problem of fractures of the carpal scaphoid lacks much of having a satisfactory solution at the present time Early recognition of these fractures by familiarity with the clinical manifestations and by the use of special roentgenologic views will help in reducing the number of cases of nonunion Even with early recognition and the present methods of treatment there will still be too many instances of nonunion or union with aseptic necrosis, producing serious permanent disability It would seem that the difficulties attendant on the treatment of the fractures closely simulate those of central fractures of the neck of the femur Complete immobilization of the fragments by some means of internal fixation at the time of the acute fracture, permitting early revascularization, may improve the results]

Under the title "Epiphyseal Pseudarthrosis," Milch⁵⁸⁸ describes an interesting condition whose recognition he feels may be of some value in explaining both the apparent failure of certain hip fusion operations and the mechanism of development of so-called coxa anteverta or the early phase of adolescent epiphysial separation at the upper end of the femur Epiphysial pseudarthrosis has been observed under the following conditions (1) after operative fusion of the hip, (2) after inflammatory ankylosis of the hip and (3) as a sequel to adolescent epiphysiolysis It may occur in any hip in which the capital epiphysis becomes ankylosed before the epiphysial plate closes The condition manifests itself as a false joint between the neck and the capital femoral epiphysis The mechanical explanation for this in cases in which the head is fused to the acetabulum is readily understood, but in cases of adolescent epiphysiolysis, in which the capital epiphysis is freely movable, other factors must be considered The author offers an interesting hypothesis to explain pseudarthrosis associated with adolescent epiphysiolysis and also adolescent epiphysiolysis itself Forces which amplify external rotation of the femoral shaft, such as overweight, trauma and conditions which decrease the resistance of the cartilage plate, for instance endocrine and other metabolic disturbances, have been proposed as causative factors, but the author states that any valid description of the mechanism must include a force which would act on the head in a direction contrary to that made necessary by the progressive anteversion of the upper end of the neck The author believes that such a force is provided by the tendon of the iliopsoas muscle as it passes over the anterior portion of the capsule of the

586 Rothberg, A S Fractures of the Carpal Navicular, *J Bone & Joint Surg* **21** 1020-1022 (Oct) 1939

587 Rothberg, A S Ununited Fractures of Carpal Scaphoid, *Am J Surg* **56** 611-613 (June) 1942

588 Milch, H Epiphyseal Pseudarthrosis, *J Bone & Joint Surg* **24** 653-662 (July) 1942

hip joint The iliopsoas tendon does not lie over the head and neck of the femur but extends only over the descending arm of the Y ligament of Bigelow In external rotation, in which the anterior portion of the femoral head is directed toward, it is seen that the iliopsoas tendon is opposed against only the epiphysal portion of the head The limit of external rotation appears to be limited not by the capsule per se but by the resistance or torsion of the iliopsoas tendon This disposition of the psoas tendon offers a rational anatomic explanation for the development of the counterforce necessary for the production of epiphysiolysis

Ghormley,⁵⁸⁹ in a careful analysis of the types and uses of bone grafts, gives some instructive data on his experience with homogenous grafts In certain instances in which a satisfactory graft cannot be obtained from the patient the use of a graft from another person is a sound surgical procedure While theoretically it is advantageous to obtain the graft from a close relative, or at least from a donor of the same blood group, practically it appears to make little difference Ghormley reports 10 successes in 18 operations with homogenous grafts, 3 of the failures being in congenital pseudarthrosis [ED NOTE—Since the introduction of the dual type of homogenous graft Boyd, Henderson and others have reported unions in congenital pseudarthrosis in the same percentage as other types of nonunion In 1 of Boyd's successful cases the graft was taken from a father by adoption, and there was no blood relationship]

Abbott and Gill⁵⁹⁰ review the use of iliac grafts for shelves and fusions of the hip and emphasize the advantages of such cancellous grafts to promote union in other locations Grafts from the ilium are easily accessible, are rapidly revascularized, contain an abundance of osteogenic material and possess sufficient stability to be used in many locations The grafts may be removed from different locations on the ilium, depending on the size and shape of the graft desired They are especially useful in filling angular defects following osteotomies and in maintaining the corrected elevation in depressed fractures of the tibial condyles The authors believe that because of their cancellous nature iliac grafts are more rapidly revascularized and revitalized than tibial grafts While they do not possess the stability of tibial grafts, grafts from the crest of the ilium are sufficiently strong to be used in many locations where it is not customary to use tibial grafts The authors' experience with grafts of this type over a period of twenty years justifies their advocating its more general use

Leavitt⁵⁹¹ reports the unusual occurrence of three ununited fractures of the ribs in a patient with an adherent diaphragm The author suggests that it would require some such unusual fixation of part of the wall of the chest to permit sufficient separation of the fragments to produce nonunion The sites of nonunion were painful Union was induced by bone grafts [ED NOTE—Disability might have been removed by resection]

McMurray,⁵⁹² in discussing the apparent increase in the number of delayed unions in military surgery, suggests the use of the nonpadded plaster cast as one of the causes He states that when a tight-fitting nonpadded cast is applied immediately after the fracture of such a bone as the tibia, the soft tissues are compressed against the bone, not permitting sufficient space for the formation of the physiologic blood clot which aids in the production of a normal amount of callus He suggests postponing the application of the cast for several days to allow the formation and beginning organization of the blood clot

589 Ghormley, R K Choice of Bone Graft Methods in Bone and Joint Surgery, *Ann Surg* **115** 427-434 (March) 1942

590 Abbott, L C, and Gill, G G Use of Cancellous Bone Grafts in Orthopedic Surgery, in *Medico-Surgical Tributes to Harold Brunn*, Berkeley, Calif, University of California Press, 1942, pp 1-11

591 Leavitt, D G Nonunion of Three Ribs, *J Bone & Joint Surg* **24** 932-936 (Oct) 1942

592 McMurray, T P Delay in Union of Fracture, *Brit M J* **1** 8-9 (Jan 3) 1942

PROGRESS IN ORTHOPEDIC SURGERY FOR 1942

PREFACE

In the preparation of this review of orthopedic surgery for 1942 the titles of 1,075 articles of orthopedic interest were selected from the *Quarterly Cumulative Index Medicus* for 1942. The number of articles reviewed and presented in this year's "Progress" is 627, or 59 per cent of the total. This is a higher percentage than in 1940 and 1941 (38 per cent and 34 per cent respectively), but the total number of articles selected this year for review is less than 1940 and 1941 (1,794 and 2,397 respectively). The smaller number of articles is due to the decrease in the volume of medical literature since the war commenced. As in the past two years, each editor has selected the articles for his section which he thinks represent the most progress and have the greatest scientific interest. The chairman or vice chairman of the editorial board has reviewed the material prepared for each section and has made certain additions and changes which seemed indicated to improve the publication as a whole.

On account of the war and the difficulties under which many of the editors have been working, the reviews of some of the sections have been slower in being returned to the chairman of the editorial board, and it was found impossible to send the whole "Progress" to the ARCHIVES OF SURGERY at one time. This has necessitated a change in the order of the sections. The preface could not be written until all sections had been submitted. It is believed, however, that in spite of the delay the quality of the reviews is up to standard and the publication will prove as valuable to its readers as the "Progress" of 1940 or of 1941.

Some of the editors last year were of the opinion that each section should have the name or names of those preparing it appearing with the section. This has been done in most instances. The members of the editorial board wish to thank again those physicians not members of the American Academy of Orthopedic Surgeons who have rendered such valuable assistance in the preparation of the material for the various sections. Special thanks are rendered to Colonel Jesse I. Sloat and his orthopedic staff at the Lawson General Hospital in Atlanta, Ga., to Major Edward C. Holscher, Major Dudley W. Smith, Captain William P. Warner Jr. and Captain Lee Schlesinger for their part in the publication, to Captain Charles H. Wilson, of Orlando, Fla., and to all the others who have helped but whose names are not mentioned.

Both style and editorial comments have again been left to the discretion of the editors, except for a few changes made by the chairman of the editorial board. It should be stated again, however, as in the preface of the "Progress" of 1940 and of 1941: "If the reader or author of any article does not agree with the editorial comment, the editorial board hopes that he will think of the remark as only one man's impression and as in no way representing the opinion of the entire editorial board."

Owing to the fact that the chairman of the editorial board is in the armed forces, it was found necessary during the year to appoint a vice chairman, who has rendered most able assistance to the chairman and made it possible for the publication to appear on time.

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LOBECTOMY OF THE LIVER

REPORT OF THREE CASES

KENNETH L. PICKRELL, M.D., AND RICHARD C. CLAY, M.D.*
DURHAM, N. C. BALTIMORE

Resection of large lesions of the liver is a relatively rare surgical procedure, and many surgeons are never called on to perform it. Though by far the commonest large resectable hepatic lesion is hemangioma, Shumacker,¹ in reviewing all the cases from the world's literature to 1942, found only 56 cases in which operation was performed and noted that no author had reported more than a single case. Nevertheless, any surgeon may unexpectedly be confronted with such a lesion, for the correct diagnosis was made preoperatively only twice among the 56 cases reported by Shumacker. Resection of the liver has been performed for such diverse conditions² as angioma, echinococcus cyst, gumma, tuberculoma, trauma, carcinoma, sarcoma, adenoma and hamartoma. The surgeon's stock of procedures should, therefore, include methods for excising large segments of the liver. It is for this reason that the present 3 cases, which demonstrate a technic for relatively bloodless resection of the entire left lobe of the liver, are reported.

The two original cardinal objections to resection of large segments of the liver were the severe hemorrhage entailed by transection of this vascular, friable tissue which retains sutures so poorly, and the fear that the function of the liver subsequently would be impaired. The latter objection was largely overcome by the studies of Turner³ in 1923, when he found the function to be perfectly normal after removal of an adenoma and a large adjacent mass of hepatic tissue weighing 2 pounds 3 ounces (992.23 Gm.). It has become generally accepted that the liver has such an enormous reserve functional capacity that huge

areas of it may be destroyed by disease before hepatic function is clinically impaired. But the problem of hemostasis in resection of the liver remains the major one.

Turner³ in 1923 summarized the methods which had been employed to effect hemostasis in operations on the liver under the following heads: (a) compression of the vessels in the free edge of the lesser omentum, (b) manual pressure on the hepatic substance at the edge of the wound, (c) placing of clamps across the liver, (d) use of an elastic tourniquet and (e) use of the cautery. A glance at some of the reported cases in which the procedure is described provides examples of these means. It will be noted that in general among the earlier cases the mass to be removed was extraperitonealized while in later reports the operation was usually entirely intraperitoneal.

In 1897 von Rosenthal⁴ reported a pedunculated angioma of the left lobe of the liver treated by transfixing the base with knitting needles. He brought these out on the abdominal wall, tied an elastic tourniquet on the hepatic side of them for hemostasis, cut off the tumor and extraperitonealized the stump. He finally cut off the extraperitonealized stump with the cautery five days after the intra-abdominal part of the procedure.

Pfannenstiel⁵ excised a hemangioma of the liver and extraperitonealized the stump by sewing Ghisson's capsule to the peritoneal wound. Beck,⁶ finding an angioma as large as a man's head in the left lobe of the liver, placed rubber catheters about its pedicle as tourniquets and brought the mass out through the wound where it was allowed to slough away with frequent débridements. Israel⁷ effected hemostasis in a case of angioma of the left lobe by placing a

* Harvey Cushing Fellow in Surgery
From the Department of Surgery, Johns Hopkins Hospital and University.

¹ Shumacker, H. B., Jr. Hemangioma of the Liver, *Surgery* **11** 209, 1942.

² Tinker, M. B. Liver Resection, *Ann. Surg.* **102** 728, 1935. Tinker, M. B., and Tinker, M. B., Jr. Resection of Liver, *J. A. M. A.* **112** 2006 (May 20) 1939.

³ Turner, G. G. A Case in Which an Adenoma Weighing 2 lb 3 oz Was Successfully Removed from the Liver, with Remarks on the Subject of Partial Hepatectomy, *Proc. Roy. Soc. Med. (Sect. Surg.)* **16** 43, 1923.

⁴ Rosenthal, J. Exstirpation einer Lebergeschwulst. *Deutsche med. Wchnschr.* **23** 54, 1897.

⁵ Pfannenstiel, P., cited by Langer, P. Erfolgreiche Exstirpation eines grossen Haemangioms der Leber. *Arch. f. klin. Chir.* **64** 630, 1901.

⁶ Beck, C. Surgery of the Liver, *J. A. M. A.* **38** 1063 (April 26) 1902.

⁷ Israel, J. Ein Fall von Exstirpation eines Lebercavernoms, *Berl. klin. Wchnschr.* **48** 662 1911.

rubber tourniquet out through the wound. Two weeks later the tourniquet was cut and withdrawn safely.

The cautery was used by von Eiselsberg⁸ in 1893 when he cauterized and packed the cut surface remaining after he had removed an angioma of the liver. Smoley⁹ occluded the pedicle of an angioma in the left lobe with an elastic tourniquet ligated it with mass ligatures, cut off the tumor with the cautery and sowed peritoneum over the stump.

Wright¹⁰ excised from the right lobe of the liver a deeply embedded primary carcinoma the size of an orange. This nodule was removed by sharp dissection and shelling out with the finger. Large vessels were clamped and ligated, and the entire wound subsequently was packed. The packing was removed three days later.

Sutures and a clamp were employed as a means of hemostasis by Turner,¹ who operated on an adenoma of the right lobe of the liver so situated that it encroached on the bed of the gallbladder. The gallbladder was removed and the cystic duct drained. After placing a long, curved stomach clamp parallel to the proposed line of excision the surgeon took alongside its blades a series of large, deep, interlocking sutures, using heavy catgut on a blunt, fully curved needle. These hemostatic sutures extended almost through the liver and were tied separately. The proposed segment of liver was then excised by cutting inside this line of sutures, and the bleeding from large vessels controlled by ligation with purse string sutures of catgut. The large gaping wound in the liver was closed by approximating the upper surfaces, under surfaces and edge of the liver respectively. The sutures employed in accomplishing this closure were locked over the previously described hemostatic sutures, thus preventing their cutting out. Kidd¹¹ removed an adenoma the size of a cricket ball from the right lobe of the liver by an almost exactly similar technic.

Benson and Penberthy¹² encountered a pedunculated tumor in the anterior edge of the right lobe of the liver, which they excised with

a v-shaped wedge of liver bearing the pedicle. They employed the cautery knife and placed omentum in the defect.

Shumacker¹ employed Kelly clamps, cautery and sutures in removing an angioma of the left lobe of the liver. The clamps were placed 1.5 cm. beyond the margin of the tumor and a small wedge of liver bearing the tumor was quickly excised by sharp dissection. The clamps cut through in the thick part of the liver, but manual pressure minimized hemorrhage. Through and through silk mattress sutures were placed within the line of clamp, and bleeding points subsequently seen when manual pressure was released were coagulated with the cautery. The bare surface of the liver was drained.

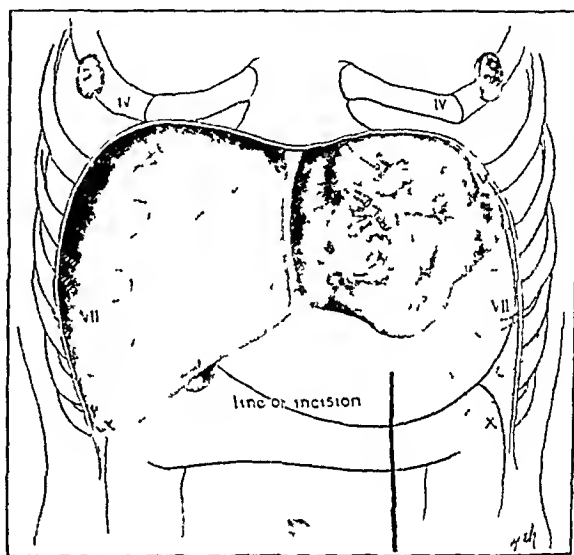


Fig 1—Topographic sketch showing position and extent of the primary carcinoma of the left lobe of the liver and the incision used to remove the lobe.

While the various ingenious procedures described are useful in resecting those lesions of the right lobe of the liver which do not include the extrahepatic biliary ducts, we have found that total extirpation of the left lobe is more easily and safely accomplished than excision of a part of it bearing a lesion. The reasons for this, as will be shown, are the thinness, relative avascularity and greater capacity for holding sutures which the insertion of the round ligament confers on the line of junction of the two lobes, together with the mobility of the lobe when it is freed from the falciform ligament. An additional advantage in the presence of an angioma or neoplasm is the wide avoidance of the tumor, a point repeatedly made by those¹³ who have cut into such a vascular tumor.

8 von Eiselsberg, F. Abtragung eines Cavernoms der Leber, *Wien klin Wchnschr* 6 1, 1893.

9 Smoley, K., cited by Pichler, K. Ein Fall von Hemangioma Hepatis. Heilung durch Exstirpation, *Ztschr f Heilk* 24 250, 1903.

10 Wright, G. Primary Carcinoma of the Liver Excised by Operation, *Proc Roy Soc Med (Surg Sect)* 16 56, 1923.

11 Kidd, F. Case of Primary Tumor of the Liver Removed by Operation, *Proc Roy Soc Med (Surg Sect)* 16 61, 1923.

12 Benson, C. D., and Penberthy, G. C. Surgical Excision of Primary Tumor of Liver (Hamartoma) in Infant Seven Months Old with Recovery, *Surgery* 12 881, 1942.

13 Horsley, J. S. Cavernous Angioma of the Liver, *Interstate M J* 23 347, 1916. von Eiselsberg⁸.

Total removal of the left lobe of the liver has been reported on two previous occasions. Keen¹⁴ resected the entire left lobe as early as 1899. The lobe was the site of a carcinoma, and was removed by burning through the pedicle of the lobe with Paquelin's cautery. This procedure required twenty to thirty minutes, the large vessels were ligated as they were encountered. The edges of the wound in the liver were then partly approximated with catgut sutures, and the

tended the left lobe so that it hung by a thin pedicle from the right lobe. In this case lobectomy was carried out simply by cutting the coronary ligaments, thus mobilizing the left lobe and clamping and tying the pedicle.

Three times within the past four months and twice within one week one of us (K. P.) has been confronted with three large lesions affecting the left lobe of the liver, for which removal of this lobe was carried out. This operation

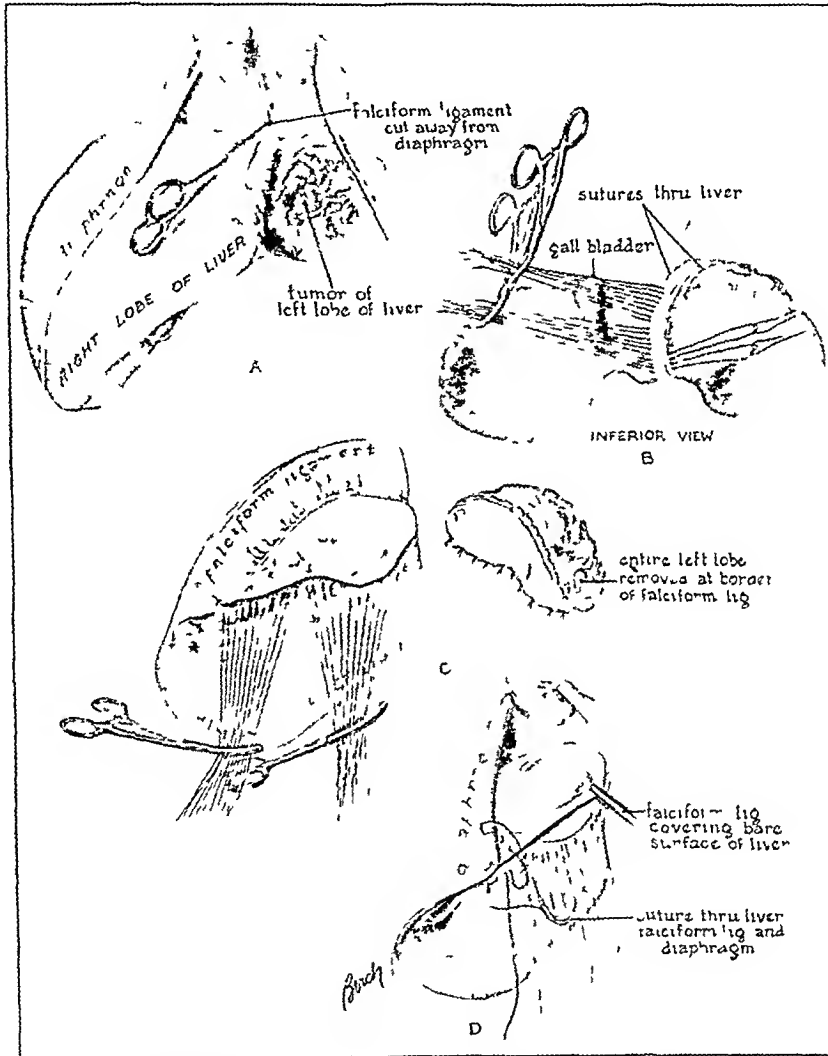


Fig. 2—Operative technique employed to remove the left lobe of the liver

remaining open part was packed with iodoform gauze. A biliary fistula persisted for over ten days after the removal of the packing. The second case was that of Peck,¹⁵ who found an angioma weighing almost 4 pounds (1.8 Kg.) in the left lobe of the liver. The tumor, apparently by its very weight, had stretched and ex-

was performed for carcinoma, hemangioma, and gumma respectively. It should not be construed that we advocate excision of gummas of the liver, but it was the opinion of the operator (K. P.) as well as of numerous observers that we were dealing with a sarcoma, a tuberculoma, or a carcinoma of the liver. An abstract of each case is presented.

REPORT OF CASES

¹⁴ Keen, W. W. Report of a Case of Resection of the Liver for the Removal of a Neoplasm with a Table of Seventy-Six Cases of Resection of the Liver for Hepatic Tumors, *Ann Surg* 30:267, 1899.

¹⁵ Peck, C. H. Cavernous Haemangioma of Left Lobe of Liver, *Surg, Gynec & Obst* 33:277, 1921.

CASE 1—Primary Carcinoma of Liver Treated by Removal of Left Lobe.—A 64 year old white man C. F. M. was admitted to the Johns Hopkins Hospital

on Aug 6, 1943. He was a farmer who had enjoyed good health until about four months prior to admission, when he began to have dull, aching pain in the upper part of the abdomen which was associated with fullness, eructation and nausea. One month later, he noticed a mass in the left upper quadrant of the abdomen, which had increased progressively in size and had become extremely tender. When the patient was in the prone position the mass presented in the left upper quadrant,

minutes after injection of histamine there was 38 degrees of free acid.

A preoperative diagnosis of a mesenteric cyst was made. Although the patient was seen by numerous observers, no one made a correct diagnosis.

Operation—On Aug 12, 1943, exploratory laparotomy was done with the patient under ether anesthesia, a left paramedian incision was made. There was no free fluid in the peritoneal cavity. Occupying the anterior-inferior part of the left lobe of the liver there was a bulging, nodular, friable, carcinomatous mass about the size of a clinched fist, there were no other nodules, the right lobe was normal. There were no peritoneal implants, and no enlarged mesenteric glands. The gallbladder, pancreas, spleen and kidneys were normal. No lesions were found in the gastrointestinal tract (fig 1).

A frozen section confirmed the diagnosis of carcinoma, and it was decided to excise the left lobe of the liver. The falciform ligament was cut about one-half inch (1 cm) from its diaphragmatic attachment (fig 2A). This step allowed the left lobe of the liver to descend to the level of the incision. With sutures of braided silk threaded on Bloodgood needles, two rows of mattress sutures were placed parallel to each other in the interlobar sulcus, extending from the inferior to the superior or diaphragmatic surface. They were inserted so that they could be tied on the inferior surface of the liver (fig 2B and C). These hemo-



Fig 3—The anterior surface of the left lobe of the liver which was largely replaced by a large, white, nodular tumor which projected from the surface of the liver. The specimen measured 14 by 10 by 8 cm.

but when he stood it shifted to the lower part of the abdomen. He had lost about 35 pounds (16 Kg) in weight.

Physical Examination—Examination revealed a thin, well preserved 64 year old white man weighing 130 pounds (59 Kg) and measuring 6 feet 4 inches (193.04 cm) in height. The abdomen was the center of surgical interest, the remainder of the examination gave essentially negative results except for evidence of loss of weight and peripheral arteriosclerosis. In the prone position there was a mass beneath the left costal margin which measured about 4 inches (10 cm) in diameter. It was well outlined, slightly tender and movable. When the patient was standing, the mass shifted to the lower part of the abdomen and could be moved to either side of the midline. The liver was not enlarged. Since the mass was so freely movable, no one suspected that it arose in the left lobe of the liver. The spleen could not be palpated. The rectum was normal.

Laboratory Data—The serologic test for syphilis gave a negative reaction. The leukocyte count was 6,600, the hemoglobin was 14 Gm. The urine showed a trace of albumin. Roentgenograms of the chest showed the heart to be normal in size, and the lungs were clear. A gastrointestinal series and a barium enema disclosed no lesions. Gastric analysis made when the patient was fasting revealed no free acid, but thirty



Fig 4—The posterior surface of the left lobe of the liver, which was largely replaced by a nodular tumor. By removing the left lobe, a relatively wide margin was obtained around the tumor. A braided silk suture is seen in the interlobar sulcus.

tatic sutures were then tied and the ends left long, after which the left lobe of the liver was removed by cutting through the liver substance between the parallel rows of sutures. This maneuver was performed in a bloodless field, and there was no soiling with bile. A

relatively wide margin of normal liver was removed with the tumor (fig 2 C)

The raw surface of the liver was then covered by bringing the free flap of falciform ligament down over it, and suturing it in this new position by using the long suture ends (fig 2 C). The left free edge of the right lobe of the liver was then fixed by suturing the falciform ligament to the diaphragm (fig 2 D). The incision was closed in layers with sutures of silk. Drainage was not employed. The operating time was thirty minutes.

Pathologic Report—The specimen measured 14 by 10 by 8 cm and consisted of the left lobe of the liver, which was largely replaced by a large, white, nodular tumor which projected from the liver surface (figs 3 and 4). The remaining parts of the liver were normal. Histologic sections showed an undifferentiated glandular type of carcinoma, presumably arising from the biliary ducts. In some areas it was seen to enter the lymphatic vessels and veins (fig 5).

Postoperative Course—This was entirely uneventful. The highest temperature recorded was 100.8 F on the

of the abdomen. It had continued to increase in size until his present admission to the hospital. He had noted the presence of the mass in the upper part of the abdomen when lying down, but when in the erect position, he felt that it shifted to the lower part of the abdomen to either the right or the left of the midline. For several months he had been annoyed by a dragging feeling, which was accompanied by a sensation of fulness and some eructation. His appetite, however, had been normal and he had not lost weight.

Physical Examination—The patient was a well preserved colored man of 62 years weighing 139 pounds (63 Kg) and measuring 5 feet 7 inches (170.18 cm) in height. There was no evidence of loss of weight. There was a well healed thyroidectomy scar. The heart and lungs were clear. The blood pressure was 160 systolic and 90 diastolic. The abdomen was slightly distended, soft and boggy. With the patient in the prone position one could see a round mass the size of a grapefruit in the left upper quadrant (fig 7). The mass was firm and slightly tender and moved freely with respiration. It seemed to arise from the left lobe



Fig 5—Low power photomicrograph showing an undifferentiated glandular type of carcinoma of the liver, presumably arising from the biliary ducts. As indicated by the arrow, in some areas the tumor entered the veins and lymphatic vessels.

second postoperative day. The incision healed by first intention, and the patient was discharged in one week. Tests for function of the liver showed no retention of bromsulfalein.

Since discharge the patient has been well except for attacks of constipation. He has gained 20 pounds (9.1 Kg) and carries out the normal duties of a farmer (fig 6). Another series of roentgenograms of the gastrointestinal tract, barium enema being given, and roentgenograms of the chest four months after the operation did not show any other lesion. Since the patient remains well, we have concluded that he had a primary carcinoma of the liver arising from the bile ducts.

CASE 2—Hemangioma of Liver Treated by Removal of Left Lobe—A 60 year old Negro man, A. McN., was admitted to the Johns Hopkins Hospital on Sept. 29, 1943. In 1929 a nodular goiter had been removed, and the patient was well until the onset of his present illness. About one year before admission the patient first became aware of a mass in the left upper quadrant

of the liver, which could not be separated from it. The right lobe of the liver could be palpated just beneath the costal margin. The mass pulsated with the aorta, but the pulsations were not expansile. The spleen could not be felt. When the patient was in the erect position the mass shifted to the lower part of the abdomen and could be moved to either side of the midline. It was when standing that the patient complained of a dragging sensation or a feeling of intra-abdominal heaviness. The remainder of the examination gave essentially negative results except for atrophy of the right testis.

Laboratory Findings—The serologic tests were strongly positive for syphilis of the blood and spinal fluid. The hemoglobin was 12.5 Gm, the leukocyte count 5,000. Blood chemistry determinations were normal. Tests of the function of the liver showed only slight retention of bromsulfalein. A series of roentgenograms of the gastrointestinal tract showed that the stomach was displaced laterally and caudally by a large

mass, the center of which was calcified (fig 8) There was no lesion within the stomach or duodenum

Operation—Operation was performed on Oct 1, 1943. The patient was anesthetized with nitrous oxide, oxygen and ether. A left subcostal incision was made, which was extended to the right side. As soon as the peritoneal cavity was entered, one could see a giant hemangioma arising from the left lobe of the liver. The mass was about the size of a grapefruit (figs 9 and 10). It was embedded in the left lobe of the liver and was surrounded by a narrow cuff or margin of normal-appearing liver. Inasmuch as there was no stalk from which it arose, in order to remove it one was forced to excise the left lobe of the liver, and the procedure was as follows:

2B and C. With a scalpel the left lobe of the liver was removed by cutting between the two rows of sutures. There was no bleeding from the cut liver surfaces. The long suture ends from the right lobe were then rethreaded, and the falciform ligament, which



Fig 7—Preoperative photographs of patient with hemangioma of the left lobe of the liver (case 2) showing the bulging mass in the left upper part of the abdomen. The patient with the gumma (case 3) presented an almost identical appearance.

previously had been cut about one-half inch from its diaphragmatic attachment, was brought down over the raw surface of the liver and sutured into this new position, the long ends of the mattress sutures being used (fig 2D). The right lobe of the liver was then

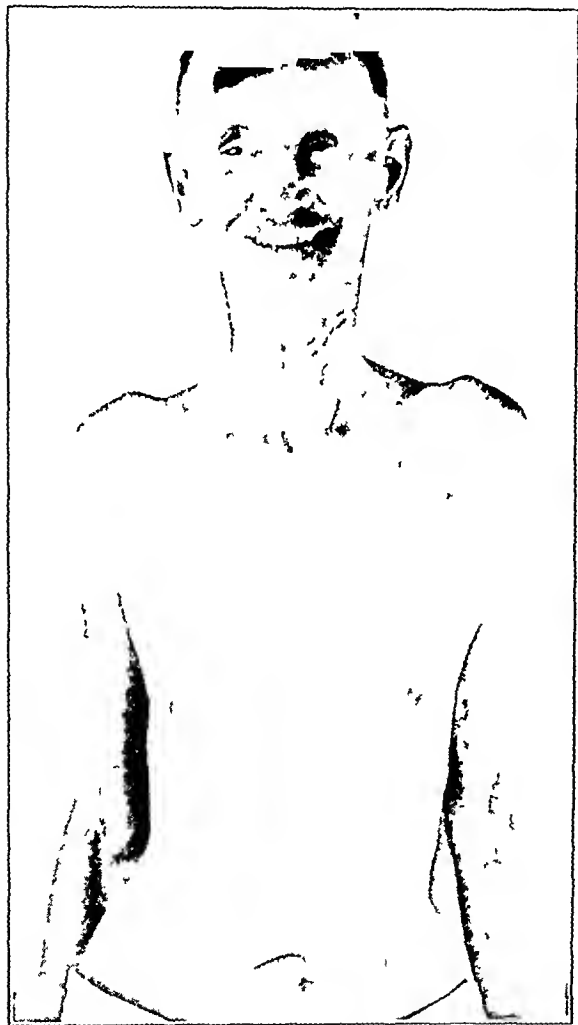


Fig 6—The patient four months after the removal of the left lobe of the liver for primary carcinoma of the bile ducts. The patient was discharged one week after operation. He has remained in excellent health and has gained more than 20 pounds.

The falciform ligament was cut about one-half inch from its diaphragmatic attachment (fig 2A). This procedure permitted mobility of the liver, so that the operator could work directly in the field. This exposure was further facilitated by extending the incision to the opposite side. With braided silk threaded on Bloodgood needles, a row of mattress sutures was inserted on each of the thinned-out, relatively avascular lines of union of the two lobes, as outlined in figure



Fig 8—Roentgenogram showing lateral and caudal displacement of the stomach due to a large hemangioma of the left lobe of the liver. Circumscribed area of calcification in the hemangioma is indicated by the arrow.

anchored to the diaphragm by suturing the diaphragmatic attachment of the falciform ligament (which had previously been cut about one-half inch from the diaphragm) to its attachment in the liver. There was no soiling with bile or blood. Several grams of sulfanilamide was placed in the peritoneal cavity, and the abdominal incision was closed in layers with sutures of silk.

Pathologic Report—The specimen consisted of the left lobe of the liver containing a large, soft hemangioma which measured 9 cm in diameter (fig 10). The hemangioma was surrounded by a cuff of liver measuring 2.5 cm, which appeared scarred and contained many large blood vessels. On section it was found to be well encapsulated, and filled with many large blood-filled spaces. The area of calcification which was seen in the roentgenogram (fig 8) was located near the center of the hemangioma.

Histologic sections showed multiple dilated, blood-containing channels with epithelium, with very little stroma between the angiomatous channels. The cuff

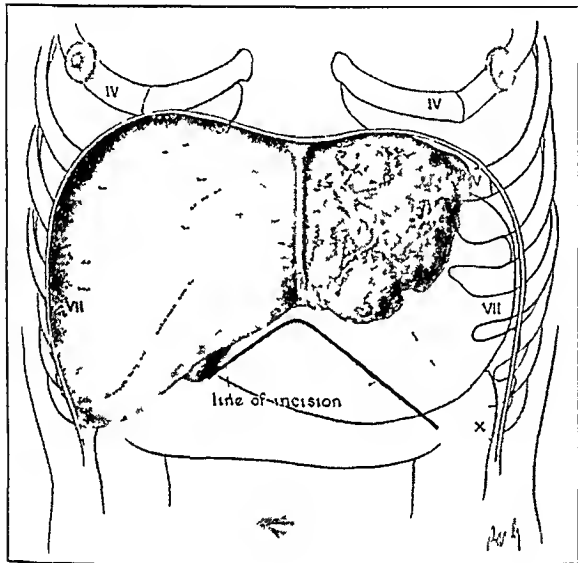


Fig 9—Topographic sketch to show the position and extent of the hemangioma of the left lobe of the liver and the incision used to remove the lobe.

of liver showed many large blood vessels leading to the hemangioma, and many bile ducts around the edge of the angoma (fig 11).

Postoperative Course—The patient's highest temperature recording was 101 F on the second postoperative day. His convalescence was uneventful, the incision healed per primam (fig 12, case 2), and he was ready for discharge two weeks after the operation. He returned to work one month after discharge from the hospital. He writes that he is receiving antisyphilitic therapy and is entirely well.

CASE 3—Gumma of Liver Simulating an Invading Carcinoma, Treated by Removal of Left Lobe—A 48 year old Negro man, W S, was admitted to the Johns Hopkins Hospital on Sept 29, 1943 because of abdominal pain.

About twenty-five years before admission the patient had a genital lesion which healed without specific therapy. He had received no antisyphilitic therapy. Three years before admission the patient had a coronary occlusion, for which he was hospitalized elsewhere. He occasionally complained of palpitation, dyspnea and precordial pain, which usually was initiated by overexertion.

The present illness began about three months prior to admission, when he began to have dull, aching pain in the upper part of his abdomen, interspersed with periods of sharp pain. He had noted progressive soreness of the abdominal wall, and about six weeks before admission felt a mass in the left upper quadrant of the abdomen. Although there were some fullness and eructation, there had been no nausea or vomiting. He had had tarry stools for a month or six weeks. He had lost about 25 pounds (11.3 Kg) during the present illness.

He also complained of a painless swelling near the angle of the jaw on the right side, which appeared with the onset of his abdominal symptoms. On one occasion it had drained purulent material. It was his opinion that the mass had caused some diminution in hearing on the right side.

Physical Examination—The patient was a chronically ill appearing-man of 48 years, weighing 128 pounds (58.1 Kg) and measuring 5 feet 8 inches (172.72 cm) in height. There was evidence of recent considerable loss of weight. The heart was enlarged 10 cm to the left of the midsternal line in the sixth interspace. The rate was slow and regular. No murmurs were heard. The blood pressure was 120 systolic and 74 diastolic.

Of primary surgical interest was the abdomen, where there was a tremendous mass occupying most of the left upper quadrant (fig 7). The mass was attached to the anterior abdominal wall. It was tender and indurated and moved only slightly with respiration. The right lobe of the liver could be palpated one finger-breadth beneath the costal margin, and the left lobe was continuous with the abdominal mass. The mass could not be moved, and there was no pulsation. There was a soft walnut-sized mass just beneath the angle of the jaw on the right side, surrounding which there were a few enlarged nodes.

Laboratory Data—Reactions to the serologic tests of the blood for syphilis were positive. The hemoglobin was 13 Gm and the leukocyte count 7,400. Roentgenograms of the gastrointestinal tract showed no intrinsic lesion of the stomach, duodenum or small intestine, and the stomach was displaced laterally and caudally. Another series showed no lesion in the large intestine. Intravenous pyelograms were normal. The stools did not contain blood.

A clinical diagnosis of retroperitoneal tumor with metastases to the cervical lymph nodes was made. The cervical mass was excised and histologic sections disclosed a tuberculous process. These microscopic changes complicated rather than simplified the picture. A diagnosis of gumma was not made by any one of either the medical or the surgical service.

Operation—On Oct 5, 1943, with the patient under nitrous oxide, oxygen and ether anesthesia a left rectus incision was made directly over the mass. The rectus muscle was invaded by the mass, therefore, we enlarged the incision both above and below, thereby entering the peritoneal cavity above and below the mass, which was still attached to the rectus muscle. The operative exposure was facilitated by excision of a large part of the anterior abdominal wall to which the tumor was attached. We could then see a tumor the size of a grapefruit arising in the left lobe of the liver (fig 13). A thorough exploration of the abdomen disclosed no other abnormalities. The right lobe of the liver was slightly enlarged but it contained no nodules. There were no peritoneal implants. The retroperitoneal spaces were normal, as were the intra-abdominal organs. We thought that we were dealing with a sarcoma, a tuber-



Fig 10—Photograph of hemangioma of liver for which the left lobe of the liver was removed. It measured 9 cm in diameter and was surrounded by a cuff of liver measuring 2.5 cm. The hemangioma was well encapsulated and contained many blood-filled spaces. The area of calcification seen in the roentgenogram is readily discernible.



Fig 11—Histologic section of hemangioma of liver showing the multiple dilated blood-containing channels lined with epithelium. There was little stroma between the angiomatous channels.

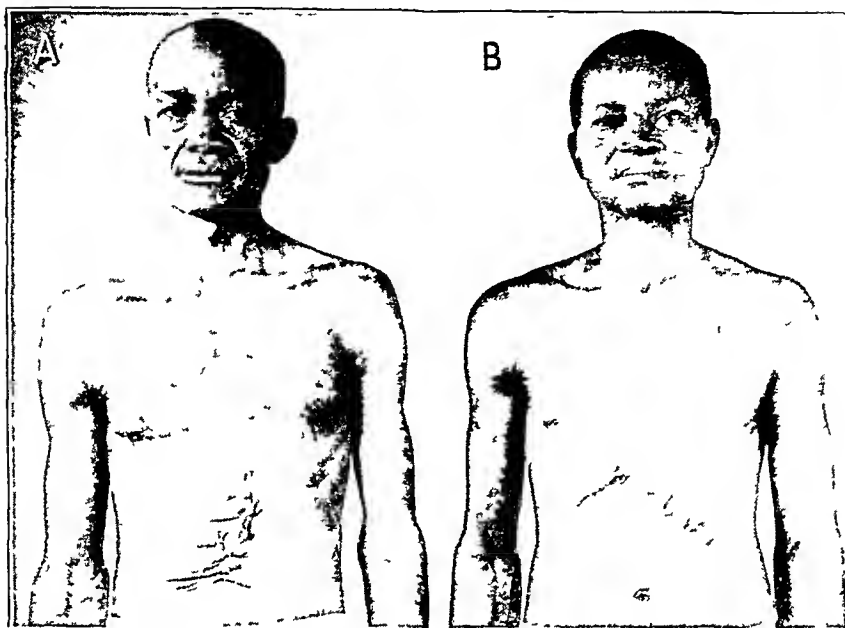


Fig 12—Postoperative photographs of patients taken two weeks after removal of the left lobe of the liver. A subcostal incision was used in case 2 (B)—hemangioma, a left rectus incision, with partial excision of the abdominal wall, was used in case 3 (A)—gumma of liver invading the abdominal wall.

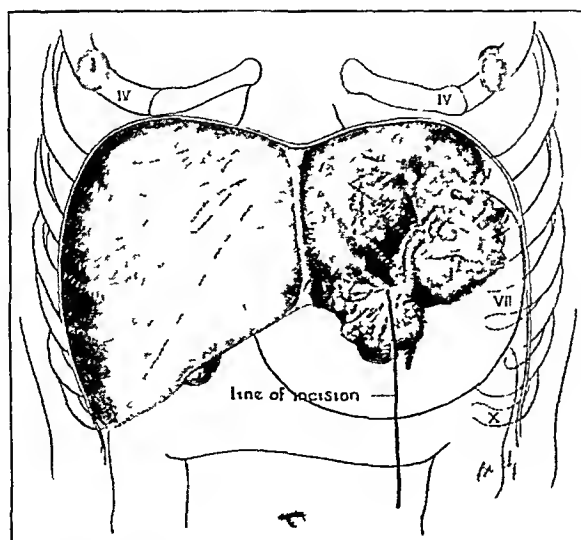


Fig 13—Topographic sketch to show the position and extent of a gumma of the left lobe of the liver and the incision used to remove the lobe.

culoma or a primary carcinoma. A frozen histologic section showed only avascular necrotic tissue. Excision of the left lobe of the liver was decided on. No one suspected that the tumor was a gumma.

Operative Technique The falciform ligament was cut about one-half inch from its diaphragmatic attachment (fig 2A). With braided silk threaded on Bloodgood needles, two rows of mattress sutures were placed in the interlobar sulcus of the liver, just to the left of the insertion of the falciform ligament. These rows of sutures extended from the inferior to the superior surface of the liver. The sutures were tied on the inferior surface and the ends left long (fig 2B and C). With a scalpel the left lobe was removed by cutting

between the two rows of hemostatic sutures. The free cuff of the falciform ligament was then brought down over the raw surface of the liver and sutured to the posterior aspect of the interlobar sulcus, the long free ends of the original mattress sutures being used. In this manner the raw surface of the liver was completely covered (fig 2D). The right lobe was then anchored by suturing the diaphragmatic attachment of the falciform ligament to the falciform reflexion on the cut surface of the liver (fig 2D). This procedure was carried out without loss of blood, and there was no soiling with bile. Several grams of sulfanilamide was placed in the peritoneal cavity, and the abdominal wall was closed in layers with sutures of silk.

Pathologic Report—The specimen consisted of the left lobe of the liver, which measured 20 by 16 by 10 cm and was partially occupied by a white nodular mass measuring 10 cm in greatest dimension (fig 14). On cutting into this mass, which was largely necrotic liver tissue, it was seen to be composed of numerous nodules of different consistency. Surrounding the major mass, although independent of it, were several smaller nodules ranging up to 1 cm in size.

Histologic sections showed the major mass to be a large gummatous area. In the more central portions of the lesion there was a great deal of necrotic liver, other areas of necrosis were caseous in appearance. On the periphery of some of the necrotic areas, and in general around the periphery of the whole lesion, there were many mononuclear cells and scattered giant cells. The mononuclear cells in places formed circumscribed hard "tubercles" in which the cells were epithelioid in appearance. Stains for acid-fast bacilli and spirochetes were negative.

Postoperative Course—The patient's convalescence was entirely uneventful. The highest temperature recorded was 99.8 F on the second postoperative day. His incision healed by first intention, and he was discharged two weeks after operation. Tests with brom-sulfalein of the function of the liver showed 8 per cent retention.

COMMENT

While resections of the liver are rather uncommon, and complete removal of the left lobe of the liver was performed in only 2 reported cases, one of us (K. P.) was called on to excise the left lobe of the liver on three occasions within the four months before this article was written and twice within a period of one week. The conditions for which the left lobe of the liver was removed were carcinoma, hemangioma and gumma.

Primary carcinoma of the liver arising in the left lobe should be treated by wide excision or preferably complete removal of that lobe, since the growth of this tumor is slow and it is late in metastasizing.¹⁶

Hemangioma occurs more commonly in the liver than in any other internal organ. Although

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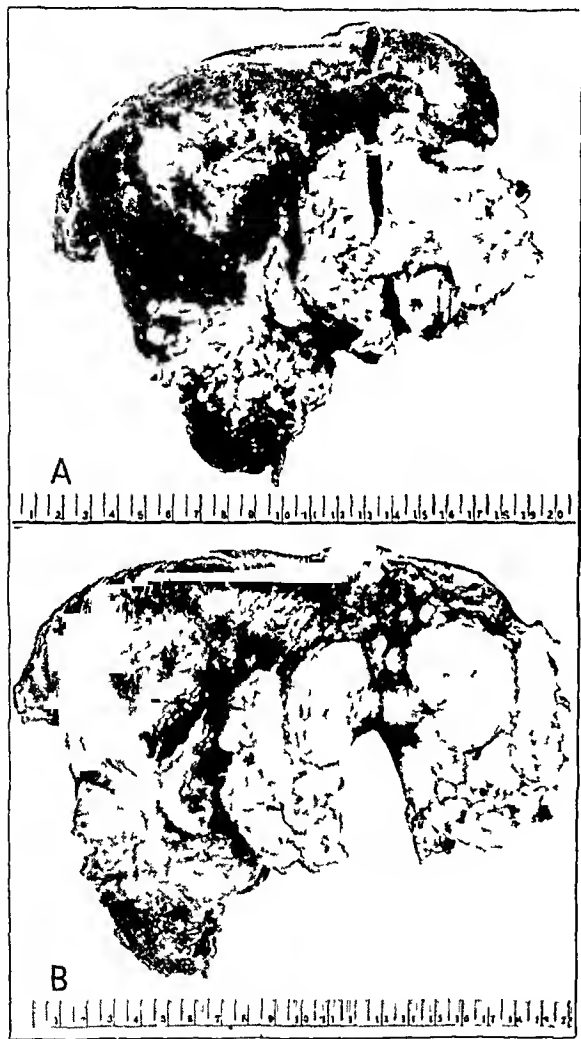


Fig 14—A shows the anterior surface of the left lobe of the liver partially occupied by a white nodular mass which had invaded the anterior abdominal wall. Histologic section disclosed the process to be a gumma. The fissures in the specimen were due to the removal of blocks of tissue for frozen and permanent section.

B shows the posterior surface of the left lobe of the liver partially occupied by a gumma, which was composed of numerous nodules of different consistency. At the time of operation, the process was thought to be either a neoplasm or a tuberculoma. Frozen section showed areas of necrotic liver, scattered giant cells and many mononuclear cells which in some areas formed "hard tubercles" in which the cells were epithelioid in appearance.

It is usually small and asymptomatic, occasionally it grows to sufficient size to cause symptoms, due not only to its position in the liver but to pressure on other organs or blood vessels. Rupture of a hemangioma of the liver occurs fairly frequently,¹⁷ carrying with it grave risk and resulting in many instances in death.¹⁸

It should not be inferred that we advocate surgical removal of gumma of the liver. In case 3 the patient might have been spared an operation if the correct diagnosis had been made. However, no one, either clinician or surgeon, had suggested this diagnosis, and even at the time of operation we thought that we were dealing with a giant tuberculoma or a neoplasm. Frozen sections did not aid in the diagnosis, and the final diagnosis of gumma was not made by the pathologists for several weeks.

The liver has such great reserve functional capacity and regenerative ability that large areas may be destroyed by disease or removed surgically before hepatic function is clinically impaired. In none of our cases was there any evidence of impaired hepatic function either before operation or after the entire left lobe of the liver had been removed. In 1 case there was slight retention of bromsulfalein ten days after operation. Favorable for extensive excision of lesions of the right lobe of the liver and for complete removal of the left lobe when it is affected is the fact that regeneration occurs promptly and almost completely. Studies in resection and regeneration have been carried out by von Meister¹⁹ and Fishback²⁰ on experimental animals in which as much as four fifths of the liver was removed, with almost complete regeneration in six to eight weeks.

Martens'²¹ study of the blood supply of the liver has shown that the right hepatic artery anastomoses freely with the branches of the left hepatic artery, so that either lobe would probably receive an adequate blood supply if the artery of the opposite side was divided. Martens also showed that the left lobe and lobus quadratus are supplied by the left branch of the hepatic artery, that the right lobe is supplied entirely and the lobus caudatus mainly by the right hepatic artery, but that the lobus caudatus also receives a small branch from the left hepatic artery. This distribution of blood supply safeguards the remaining liver substance in case radical resection of either lobe is necessary, with sacrifice of the blood supply of that side.

SUMMARY AND CONCLUSIONS

Total extirpation of the left lobe of the liver has been reported twice. Partial excisions have been reported on numerous occasions. Removal of the entire left lobe of the liver is advocated, for it has been found to be more easily and safely accomplished than local excision of a large part of it containing a lesion.

Complete removal of the left lobe of the liver has been performed on 3 patients. Mobilization of the liver was obtained by dividing the falciform ligament near its diaphragmatic attachment. Hemostasis was accomplished by inserting two rows of mattress sutures of braided silk in the interlobar sulcus, which were tied on the inferior surface the ends being left long. The left lobe was then resected. The raw surface of the right lobe was covered with the falciform ligament. The right lobe was then firmly attached to the diaphragm the long suture ends being employed as figure-of-8 stitches.

Function of the liver after total extirpation of the left lobe has not been impaired.

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FRACTURES OF THE CARPAL SCAPHOID BONE IN INDUSTRY AND IN THE MILITARY SERVICE

LIEUTENANT COMMANDER M G HENRY (MC), USNR

In a large industrial organization injuries to the wrist outnumber other injuries by a wide margin. These injuries include sprains that heal by themselves, sprains that become chronic and so-called "sprain fractures." Aside from these there is also the all too common "special case" which becomes progressively worse regardless of treatment. Carefully taken roentgenograms usually reveal a scaphoid bone with an ununited fracture. This type of injury presents varied problems. It is not alone a painful handicap to the patient and a perplexing case to the physician but it is a decidedly trying case for the Accident Commission and becomes a serious economic liability in the yearly budget. In the military service the patient with a fractured scaphoid becomes a "complainer" and is not only a handicap to the service but, more important, exceedingly bad for the morale of the men in camp.

REVIEW OF LITERATURE

All writers on fractures of the scaphoid bone agree that this is one of the most easily overlooked injuries and, therefore, one of the most neglected and most frequently incorrectly diagnosed and improperly treated.

In 1907 Thomas Dwight¹ called attention to the weak internal structure in the middle region of this bone, the density of the structure at each end, and the fact that the proximal end has more strength than the distal end. In some scaphoids there are evidences of incomplete union of two distinct elements. There may be numerous anomalies in the scaphoid, as in other bones, and these anomalies are easily revealed in roentgenograms. Since this paper was completed I have accidentally discovered an anomalous scaphoid which was not only fractured but found to be congenitally fused with the greater multangular bone. A brief report of a case of this interesting anomaly will be made in a later paper.

Davidson and Horowitz (1938)² stated the belief that total excision of the scaphoid is the operation of choice in badly comminuted frac-

tures, and that early excision results in a painless and normally functioning wrist with little or no deformity. They recommend total, not partial, excision. Five of 8 cases of nonunion with pain and disability in which they performed total excision showed excellent results. Our studies have led my colleagues and me to agree with the conclusions of these authors as to the advisability of this procedure.

Brittain³ (1938) emphasized the fact that fracture of the scaphoid is the most common injury to the carpal bones, and decidedly the most neglected. However, one cannot agree with this author's recommendation of removal of the entire proximal row of carpal bones as the operative treatment for ununited fractured scaphoids. Such a radical procedure must greatly interfere with the mechanics of the joint and weaken its function decidedly.

Phillip Wilson⁴ described the relatively poor blood supply in carpal bones. He brought out the fact that fractures of these bones were generally intra-articular and that the fragments were bathed in synovial fluid.

Lack of all periosteal callus as an important factor in causing slower fusion of the fractured fragments was brought out by Robert Johnson⁵ in 1927.

In cases of dislocation of the fractured scaphoid Kellogg Speed⁶ in 1924 recommended early operative removal, stating that this procedure promised the greatest return of function.

Our observations agree with those of Obletz and Holstein,⁷ who stated that there is a characteristic tendency of fractures of the scaphoid to result in nonunion, and that this becomes one of the most disabling and serious afflictions of the wrist. From their anatomic studies of the scaphoid bone they show the relationship between

3 Brittain, H. A. Fracture of the Carpal Scaphoid, *Brit M J* 2 671 (Sept 24) 1938.

4 Wilson, P. D. Experience in the Management of Fractures and Dislocations, Philadelphia, J. B. Lippincott Company, 1938, pp 40 and 41.

5 Johnson, R. W., Jr. A Study of the Healing Processes in Injuries to the Carpal Scaphoid, *J Bone & Joint Surg* 9 482 (July) 1927.

6 Speed, K. The Fate of the Fractured Carpal Navicular, *Ann Surg* 80 532 (Oct) 1924.

7 Obletz, B. E., and Holstein, B. M. Non-Union of Fractures of the Carpal Navicular, *J Bone & Joint Surg* 20 424 (April) 1938.

1 Dwight, T. A Clinical Atlas. Variations of the Bones of the Hands and Feet, Philadelphia, J. B. Lippincott Company, 1907, pp 3 and 4.

2 Davidson, A. J., and Horowitz, M. T. An Evaluation of Excision in the Treatment of Ununited Fractures of the Carpal Scaphoid Bone, *Ann Surg* 108 291 (Aug) 1938.

the relatively inadequate circulation and the high incidence of nonunion. There is a narrow ridge running obliquely around the dorsal surface in which are found the arterial foramina through which the vessels supply the bone with nourishment. Fracture through the middle portion could interrupt the blood supply to the fragments, thus leading to necrosis. The synovial fluid pres-

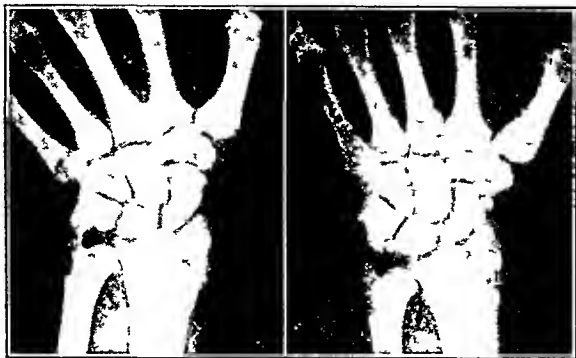


Fig 1—A striking photograph to bring out the rigid rule in technic that the hand must be in sharp ulnar deviation when roentgenograms are taken of the wrist. On the right, the normal anteroposterior view shows no evidence of fracture. On the left, same case, with the hand in sharp ulnar deviation a typical well marked fracture of the middle third of the scaphoid is brought out.

ent, they stated, exerts no serious action. There is some disagreement on the latter point. Wilson believes that its presence retards healing of the bone.



Fig 2—Complete malunion of fractured middle third of scaphoid and markedly necrosed bone with absorption and nonunion. The picture shows the result of total excision of the scaphoid. A perfect functional result was obtained in this case.

Bone grafting is regarded by some as highly effective. B. S. Adams⁸ instituted this procedure in 1928, obtaining perfect anatomic and functional results. The exact technic may vary,

⁸ Adams, B. S. Fractures of Bones of Hand and Fingers, Minnesota Med 12:515 (Sept.) 1929.

but the operation is always essentially the same. A piece of tibia trimmed to proper size bridges the fracture line. The scaphoid fragments are prepared either by grooving or by boring a hole in the bone, care being taken not to injure the articular surfaces. A graft is preferred to a bone peg because it stabilizes the fragments more effectively.

Writers on this subject are in agreement as to the advisability of operative measures in treating these fractures. There is some disagreement as to the best treatment but the consensus is that excision of the bone in cases of nonunion of fractures results in relief of symptoms and nearly normal function of the wrist.

There is almost unanimous agreement that final results in these injuries must be judged



Fig 3—This picture shows typically what we believe is a critical fracture through the inner middle third of the scaphoid resulting in nonunion and necrosis of the bone, even though every form of conservative treatment was tried out. Total excision of the scaphoid bone resulted in satisfactory function.

clinically and not by roentgenograms alone. A roentgenogram may show complete union of the bone, but clinically the wrist may still be painful and ankylosed and, viewed from an industrial angle, a definite handicap.

AUTHOR'S CASES

In this report I submit 12 cases of fractured carpal scaphoid from a five year survey of work done in a large industrial plant. The histories of the cases are omitted. The work in the industry was hazardous, and yet in the military service my survey of only four months shows nearly twice as many cases. The large number of men from all over the country together with

the severe commando type of activity makes for the greater number of cases in the army

Of the 12 cases in industry over a five year period, 9 patients recovered completely with exacting but conservative management. They regained full painless function of the injured wrist in an average time of twelve weeks. Three patients, or 25 per cent, required surgical inter-

embarkation base I was able to find 22 cases of fractured scaphoid. Practically all of these patients gave the same history of falling on the hand during rigorous exercise maneuvers. The time elapsed between their injury and the day of examination ranged from one day to three years. The table brings out the evident chronicity of pain and malfunction in these cases over long

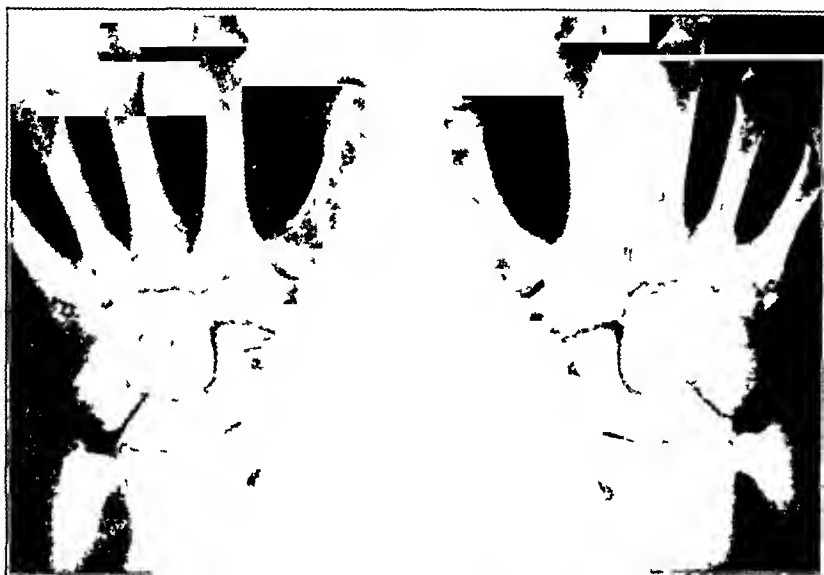


Fig 4—Fracture of the middle third of the scaphoid bone. Roentgenograms of both wrists show that when there is an anomalous ridge in one wrist there is a definite fracture through the anomalous ridge in the other wrist.

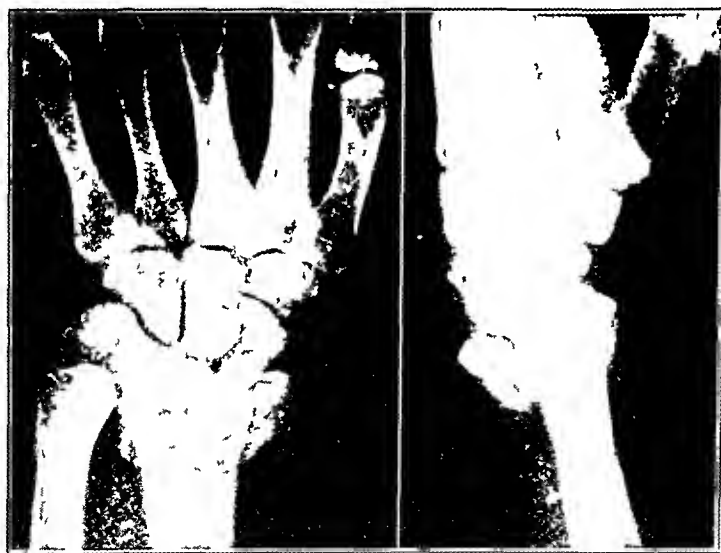


Fig 5—This picture shows severe dislocation in the carpal bones, also a fractured radius with a severely fractured scaphoid. Owing to excessive and severe injuries in this wrist, it was thought that the scaphoid would have to be removed. Three months later, when more severe pathologic processes elsewhere in the body were treated, the scaphoid was noted to be entirely healed showing that even though other bones of the wrist were involved, circulation to the scaphoid per se was intact and union occurred.

vention, 2 for nonunion following prolonged conservative treatment and 1 for marked displacement of the lateral fragment.

During a four month period, from April through July of 1943, at a large receiving and

periods. Seventy-three per cent of the patients suffered from fracture through the middle third of the bone, while 22 per cent had fractures of the outer third and only 5 per cent of the inner third. All of these patients had pain in the wrist,

especially on hyperextension of the hand and all had weakness in gripping. There were 7 cases (32 per cent) of definite nonunion. In all of these the fractures were of the middle third of the bone and the patients had total loss in dorsiflexion and pain on gripping. The average age of the patients in this survey is 25 years. A table of the results of this survey of cases at a United States Navy destroyer base follows:

COMMENT ON CASES

A thorough analysis of our cases has convinced us that no one set of rules can ever be ideal for this industrial as well as military prob-

Naturally, pain itself automatically becomes a most efficient splint.

It is felt that the end result does not depend on immobilization, rest or any other conservative treatment, but rather on the site of the injury and whether or not this injury has destroyed or impaired the already poor circulation to the scaphoid bone. It has been our policy to operate as early as possible after the diagnosis is made, if operation is to be done, because we feel that this gives the best ultimate functional result. Undoubtedly, if one delays it will not only be necessary to deal with a fractured scaphoid *per se*, but also with subsequent chronic changes

Data in Twenty-Two Cases of Fracture of the Carpal Scaphoid Bone at a United States Reviewing Station Destroyer Base from April 1 to August 1, 1943

Etiology	Age	Time Elapsed Since Injury	Site of Fracture	Weakness in Gripping	Pain	Loss of Motion—Permanent Injury
Fell on hand	24	3 years injured again	Mid $\frac{1}{4}$	Yes	Yes	Loss in dorsiflexion nonunion
Fell on hand	27	1 day	Mid $\frac{1}{4}$	Yes	Yes	Yes
Fell on hand	26	1 day	Outer $\frac{1}{4}$	Yes	Yes	Slight
Fell on hand	29	1 month	Outer $\frac{1}{4}$	Yes	Yes	Healing callus
Struck wrist	25	1 day	Mid $\frac{1}{4}$	Yes	Yes	Fracture not complete
Struck wrist	22	1 month	Mid $\frac{1}{4}$	Yes	Yes	Fracture not complete
Fell on hand	21	2 months	Mid $\frac{1}{4}$	Yes	Yes	Nonunion yes
Fell on hand	23	1 day	Mid outer $\frac{1}{4}$	Yes	Yes	Incomplete fracture
Fell on hand	19	4 days	Mid $\frac{1}{4}$	Yes	Yes	Loss in dorsiflexion
Fell on hand	26	6 weeks	Mid $\frac{1}{4}$	Yes	Yes	Callus union good incomplete fracture
Fell on wrist	26	1 month	Mid $\frac{1}{4}$	Yes	Yes	Incomplete fracture
Fell on hand	20	7 months	Mid $\frac{1}{4}$	Yes	Yes	Nonunion with absorption pain and swelling
Fell on wrist	18	2 months	Outer $\frac{1}{4}$	Yes	Yes	Healing all right
Run over by roller skate	18	1 day	Outer $\frac{1}{4}$	Yes	Yes	Incomplete fracture
Fell on hand	22	2½ months	Outer $\frac{1}{4}$	Yes	Yes	Incomplete fracture
Fell on arm	21	1 day	Inner $\frac{1}{4}$	Yes	Yes	Incomplete fracture
Fell on hand	33	7 months	Mid $\frac{1}{4}$	Yes	Yes	Nonunion
Fell on hand	30	3 years	Mid $\frac{1}{4}$	Yes	Yes	Nonunion with bone absorption and separation
Fell on wrist	19	3 months	Mid outer $\frac{1}{4}$	Yes	Yes	Incomplete fracture healed
Fell on hand	35	3 years	Mid $\frac{1}{4}$	Yes	Yes	Pain nonunion
Fell on wrist	22	1 day	Mid $\frac{1}{4}$	Yes	Yes	Incomplete fracture
Fell on hand	20	1½ years	Mid $\frac{1}{4}$	Yes	Yes	Nonunion with bone absorption crepitus total loss in dorsiflexion

lem. Each fractured scaphoid must be treated as an individual problem if satisfactory results are to be obtained. We do not believe that immobilization of the part can ever warrant a prognosis of the end result. A study of the anatomy of the wrist strengthens this belief. Any surgeon who operates on the carpus knows only too well how closely knit are the integral structures that make up the wrist joint. Nowhere else in the body are there such strong, short, closely knit ligamentous structures as those which hold these two rows of bones together, because nature here dictates the greatest amount of function compatible with ample protection and strength. For all these reasons it seems futile to attempt individual immobilization of an integral small bone in such an already closely knit organization.

sclerosis, calcification of the soft tissues and arthritic changes. When operation is performed late a partial ankylosis results and thus, to a certain degree, a permanently painful wrist joint.

We believe fractured scaphoids are so often overlooked because sufficient importance is not given to the complaint of "sprained wrist." Every physician has heard a patient say, "I fell on my hand and got a kink in my wrist, just a sprain." When this simple sprain does not get well, since a proper diagnosis has not been made roentgenograms are taken with the resultant diagnosis of a fractured scaphoid. The bad feature of this type of case is that chronic changes have occurred in the bone, and no matter what treatment is used the outcome will be most unsatisfactory. In addition the most important

as well as the most commonly used, function of the hand—that of gripping—is especially painful and weakened for a long time after the injury. Many physicians as well as patients cannot understand why after a so-called simple injury to the wrist the hand cannot be dorsiflexed and cannot grip ordinary objects with the same strength as before.

Any dislocation of the scaphoid we believe should be treated by total excision of the bone, because of the fact that minute as well as vital vessels are destroyed and the resulting dead bone becomes a painful foreign body. We stress the fact that circulation plays the predominant role in determining the outcome. If the already poor circulation of the scaphoid is further impaired by injury, there occurs a slow sterile necrosis. The dead bone is gradually absorbed

and may be mistaken for a fracture in roentgenograms. This anomalous ridge occurs near the middle third of the bone. One roentgenogram may give it the appearance of a fracture but another one taken with the hand in sharp ulnar deviation will show the true condition.

Attention should be called to the technic of taking the roentgenograms. When it is suspected that the scaphoid bone is fractured there should be extreme ulnar deviation of the hand in the roentgenograms; this position will bring out the bone in its entirety. In an instance in which this technic was not employed a negative roentgen report justified us in allowing the patient to return to work in a reasonable time. He returned to us later with a painful malfunctioning wrist. A roentgenogram made with the hand in sharp ulnar deviation showed an old

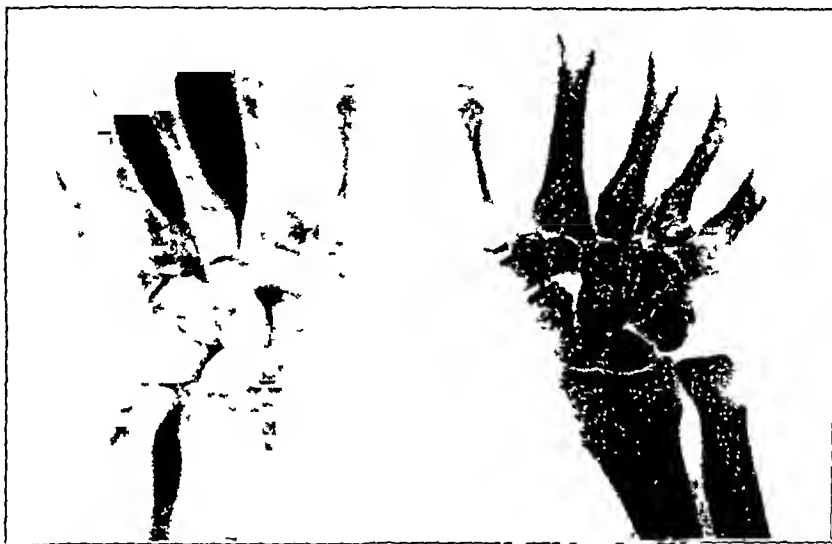


Fig. 6—This picture brings out the importance of checking both wrists for comparison, especially when there is an anomalous ridge of bone present which is suggestive of fracture, however, if, as this picture shows, such a ridge of bone is present similarly in both scaphoids, a negative diagnosis is established.

and replaced by fibrous tissue. Many an unhealed fracture line through a scaphoid bone is called healed when it is filled with dense fibrous tissue producing a syndesmosis rather than a synostosis.

We feel that interposition of the soft parts in this type of fracture has nothing to do with nonunion. It is also possible that the fractured scaphoid may be part of a picture of another fracture involving the hand and wrist, as for example fracture of the scaphoid is often associated with a simple Colles fracture. It is important in reducing a Colles fracture not to leave the most important part of the wrist unattended, because this one small bone may cause the patient more trouble than the longer fracture. We should like to call attention to the anomalous scaphoid which often is suggestive of a fracture

fracture of the middle third of the scaphoid bone with complete nonunion and necrosis. We were then compelled to do a total excision, following which a satisfactory functional result was attained.

Figure 1—the anteroposterior view—showed a fractured radius but nothing more. At a later date a view with marked ulnar deviation showed in addition a fracture of the middle third of the scaphoid. We believe that in any puzzling injuries of the wrist, roentgenograms with the hand in this position should be made as a matter of routine.

CONCLUSIONS

This survey gives the comparative frequency of fractured scaphoid bones in industry and in a large military naval base. Fractures of the carpal scaphoid are the most frequently missed of all

injuries to the wrist and therefore are the most neglected. They constitute a most serious industrial as well as military problem.

All sprains of the wrist not showing progress within a week should be examined roentgenographically.



Fig 7—A two and a half year old fracture of the middle third of the scaphoid with nonunion and separation and loss of function. This picture was taken in a case at a United States Navy destroyer base.

When roentgenograms are taken the hand should be in extreme ulnar deviation at the wrist joint. This procedure throws the scaphoid into clear view. Many fractured scaphoids are missed because this technic is not followed.

Complete fracture through the middle to inner third of the scaphoid with any degree of displacement should always be treated by complete excision, after swelling of the wrist has subsided. Fractures of the middle to inner third affect the nutrient arteries, and since the circulation is already poor, any impairment of this circulation is detrimental to firm, bony union.

When the fracture of this bone is a mere line, and the fragments of bone are in good apposition, with no displacement and little if any,

comminution, the treatment is conservative consisting of immobilization, diathermy, whirlpool baths and passive and active movement.

When the scaphoid bone is seriously comminuted, and especially when the comminution involves—as it usually does—the outer third, early surgical treatment is advised. All the affected part should be excised, the main bone structure being left unmolested.

Any dislocation of the scaphoid should be treated by total excision of the bone.

Pain and weakness on gripping, as well as local pain or dorsiflexion, indicate a lesion of the scaphoid.

Any crushing of the scaphoid should be treated by complete removal of the bone. Fracture of the scaphoid is a commonly misdiagnosed condition, many so-called sprained wrists or sprained fractures are actually fractures and too frequently there is nonunion because of poor circulation in the bone.



Fig 8—Three year old fracture of the middle third of the scaphoid with absorption of bone. The patient suffered severe pain and loss of function (Preisser's syndrome). The picture is of a case at a United States Navy destroyer base.

In a five year industrial survey there was an incidence of 25 per cent of nonunion in fractured scaphoids while in a large military base with more cases to report the percentage was 32.

HEAT AND MUSTARD GAS BURNS

A COMPARISON

LIEUTENANT COLONEL AMOS R KOONTZ

MEDICAL CORPS, UNITED STATES ARMY

The object of this series of experiments is to make a comparison of the pathologic picture of heat burns and that of mustard gas burns, with a view to determining whether the same methods of treatment are applicable to the two types of burns

HISTORICAL AND THEORETIC ASPECTS

Since the introduction of mustard gas into modern warfare during the first World War there has been much speculation as to the exact nature of mustard gas burns. There has been a general feeling that mustard gas burns are more persistent than heat burns of the same degree of intensity and that the healing process is slower. Little evidence has been adduced to prove this point.

It is true that Warthin and Weller,¹ who published a rather extensive monograph on mustard gas poisoning in 1919, did produce some evidence to support the general view. The following direct quotation is a summary of their findings:

It differs from a heat burn in the absence of thrombosis, in the greater degree of fluid exudation, in the greater moistness of the affected area and in the fact that necrosis as shown by the loss of nuclei requires hours, or even days, for its complete development. The coagulated, shrunken and cooked appearance of the tissues in heat burns is not apparent in the tissues of mustard gas burns.

The slow healing is probably chiefly due to vessel injury and the relatively slight leucocytic demarcating infiltration. In this respect the lesion is strikingly like an X-ray burn of the skin.

In spite of this pathologic study, there has been a feeling among a number of clinical surgeons who had wide experience with mustard gas burns during the first World War that such burns do heal readily and rapidly if infection is kept out and that, all circumstances being considered, the condition is no more prolonged, and the healing is no more delayed, than with heat burns of the same degree of intensity.

The presence of thrombosis in the small blood vessels in heat burns and its absence in mustard

gas burns have been stressed by Warthin and Weller¹ and have been regarded as of considerable pathologic importance. However, MacCallum² in his discussion of heat burns stated that "thrombosis of the minuter vessels has been described by several, but others have failed to demonstrate any such occlusion, and it can hardly play an important part." Adam³ and Delafield, Prudden and Wood⁴ spoke of the thrombosis of blood vessels in third degree heat burns but made no mention of it in first and second degree burns. It seems highly probable that the problem of thrombosis and the factors causing it are no different in burns from either heat or mustard than they are elsewhere. Sufficient injury of any sort—mechanical, thermal or chemical—to any blood vessel causes thrombosis. It is quite likely that thrombosis in the vessels of areas burned with either heat or mustard is dependent on the amount of injury produced by the agent concerned.

A new feature has been introduced into the comparative study of heat and of mustard gas burns by the report from England⁵ that as late as twenty-one days after exposure there are signs of "death pyknosis" in the nuclei of invading fibroblasts. Therefore, the English investigators believe that mustard or "something" stays in the skin up to twenty-one days and continues to cause damage. Control burns with heat and with chemicals did not produce the later death and pyknotic changes noted with mustard burns.

Obviously, from the foregoing considerations it is not certain that there is any essential difference in the nature of heat burns and of mustard gas burns. Whether or not such a dissimilarity exists and, if it does exist, what the nature of the difference is are not matters of

2 MacCallum, W. G. *A Textbook of Pathology*, ed 5, Philadelphia, W. B. Saunders Company, 1934, p. 360.

3 Adam, J. G. *The Principles of Pathology*, ed 2, Philadelphia, Lea & Febiger, 1910, vol 1, p. 290.

4 Delafield, F., Prudden, T. M., and Wood, F. C. *A Textbook of Pathology*, New York, William Wood & Company, 1921, p. 10.

5 Walton, D. C. Personal communication to the author.

1 Warthin, A. S., and Weller, C. V. *The Medical Aspects of Mustard Gas Poisoning*, St. Louis, C. V. Mosby Company, 1919, pp. 79 and 80.

purely theoretic or speculative interest. If there is no difference between the two types of burns, then the methods of treating heat burns are equally applicable to mustard burns. If a dissimilarity does exist, it is highly probable that the treatment will have to be varied somewhat. The object of this work is to determine this point.

PLAN OF EXPERIMENTAL STUDIES

OUTLINE OF EXPERIMENTS

During the course of this investigation, the following four series of experiments were made:

1 A comparative study (gross and microscopic) of heat burns and of mustard burns on dogs' skin, in which both stock dogs and Mexican hairless dogs were used, the latter being employed because their skin blisters and thus more nearly approximates human skin.

2 Experiments with goats to determine the relative amount of capillary thrombosis in heat burns and in mustard burns.

3 Experiments with goats to determine the extent of the inflammatory area beyond the point of application in heat burns and in mustard burns.

4 Experiments with rabbits to determine the relative healing time of mustard burns and of heat burns.

GENERAL PROCEDURE

Cutaneous burns were produced, as nearly as possible of equal degrees of intensity, by heat and by mustard. The heat burns were caused by applying a water-heated metal cylinder 1 cm in diameter to the skin for three minutes. The temperature used was 80 C. The mustard burns were produced by applying liquid mustard to the skin by the usual rod method, except that a glass rod 1 cm in diameter was used. Two applications were made in each instance.

Since details of procedure applicable only to certain experiments will be of greater value in the actual consideration of those experiments, such details have been incorporated in the records of the experiments to which they pertain.

RESULTS OF EXPERIMENTS

I. COMPARATIVE STUDY OF HEAT BURNS AND MUSTARD BURNS ON DOGS' SKIN

In this series of experiments 14 stock dogs and 4 Mexican hairless dogs were used.

Gross and General Observations—Just after exposure the heat-burned areas appeared red with a slight swelling about the outer parts. On the Mexican hairless dogs, small blisters appeared in these areas. Scabs formed within twenty-four to forty-eight hours, and these were depressed

and hard. The scabs usually came off in from sixteen days to three weeks, leaving healthy scars.

Mustard when first applied caused a blanching of the area. This persisted for three or four hours, and then the area started to swell. Small blisters appeared in about twenty-four hours on the Mexican hairless dogs. The areas became scabbed about the fifth or the sixth day. The scabs were not as hard and depressed as those on the heat burns, and generally the surrounding areas were more swollen. The scab remained in most cases from sixteen days to three weeks and when it was lifted off a healthy scar was found underneath. The healing time was approximately the same with both types of burns.

The periods of healing of the burns as shown by the microscope were slightly longer than those observed with the naked eye, because there was generally a small area in the center of each burn not entirely healed that was not apparent in a gross examination. Sections of burns were taken beyond the healing time in order to note any differences in healed scars.

Resumes of the microscopic observations made after different intervals on (1) stock dogs and (2) Mexican hairless dogs are given in the sections to follow. In order to avoid confusion all data for the stock dogs are presented first. In the reports on burns of stock dogs, most of the descriptions (those not otherwise specified) of stages of the burns are composite descriptions of sections taken from burned areas of all the dogs studied. In some instances, however, a description of the burns of a specific dog is used and in these cases the specific dog is indicated by its serial number. These specific cases are included in order to show that there are individual differences in the rate of change in the pathologic process and that because of these differences it does not always show the progressive picture that might be expected.

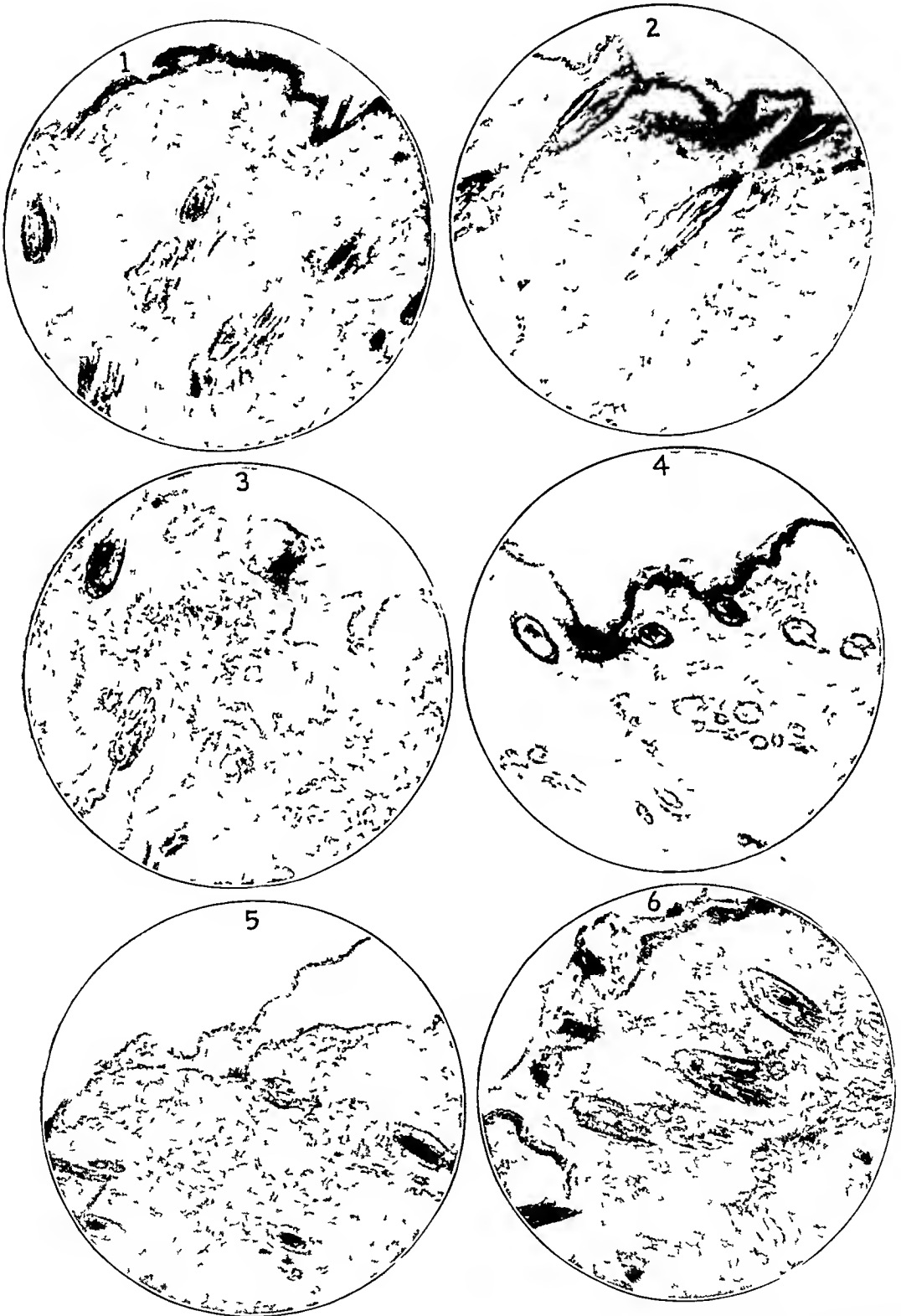
Microscopic Observations on Stock Dogs

ONE HOUR—Heat Burns (Fig 1) The nuclei of the epithelium were pyknotic and there was fusion (coagulation?) of the epithelial cells. The nuclei of the capillary endothelium were pyknotic, while those of the sebaceous glands were only slightly pyknotic. The horny layer was destroyed, and most of the blood vessels had collapsed.

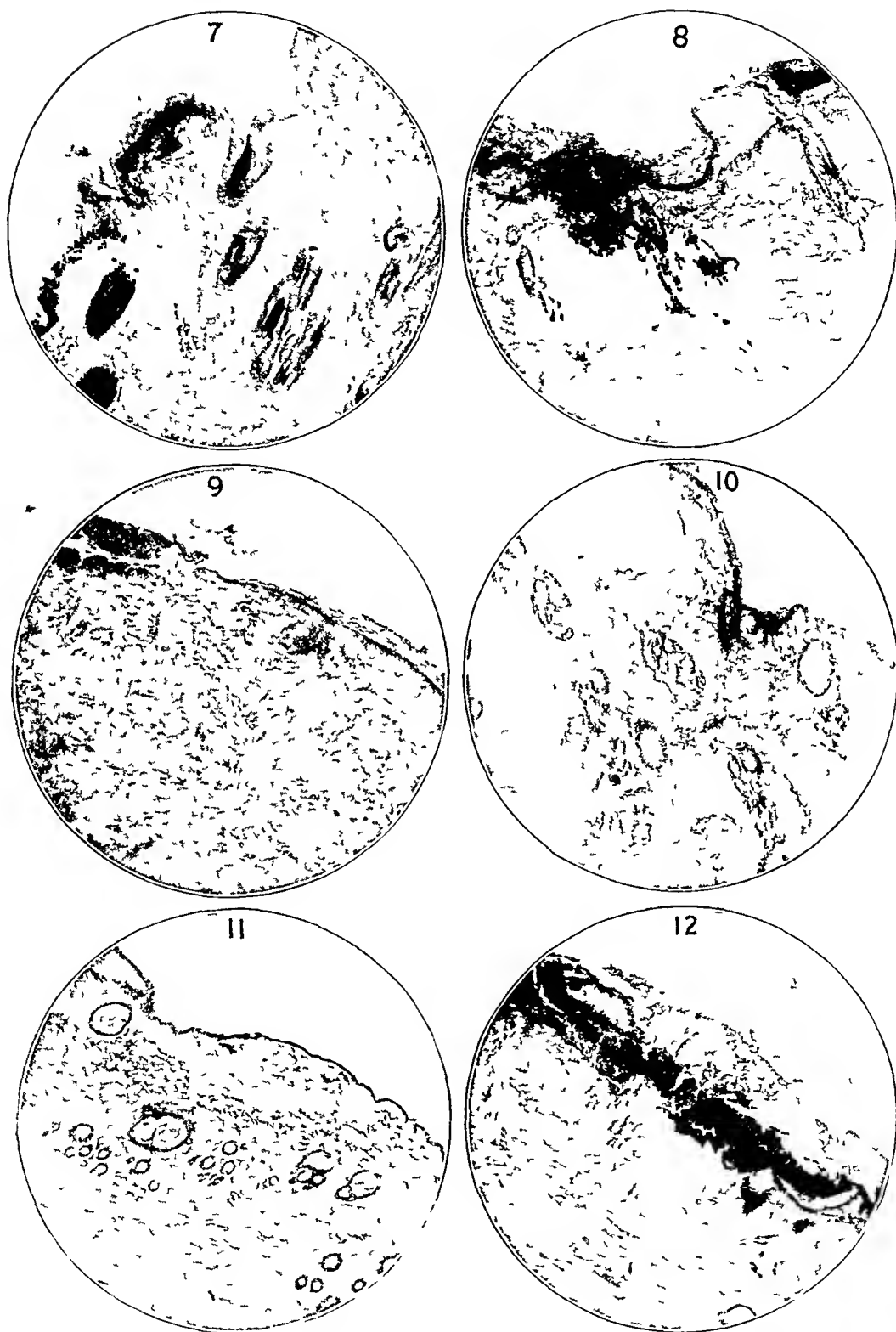
Mustard Burns (Fig 2) The epithelium was rather normal in appearance, the nuclei of the epithelium were only slightly pyknotic, and the nuclei of the capillary endothelium were pyknotic. The capillaries contained many polymorphonuclear leukocytes, a few polymorphonuclear leukocytes were in the tissues, and most blood vessels had collapsed.

TWO HOURS—Heat Burns (Fig 3) The picture is the same as that of the one hour burns except for considerable leukocytic reaction.

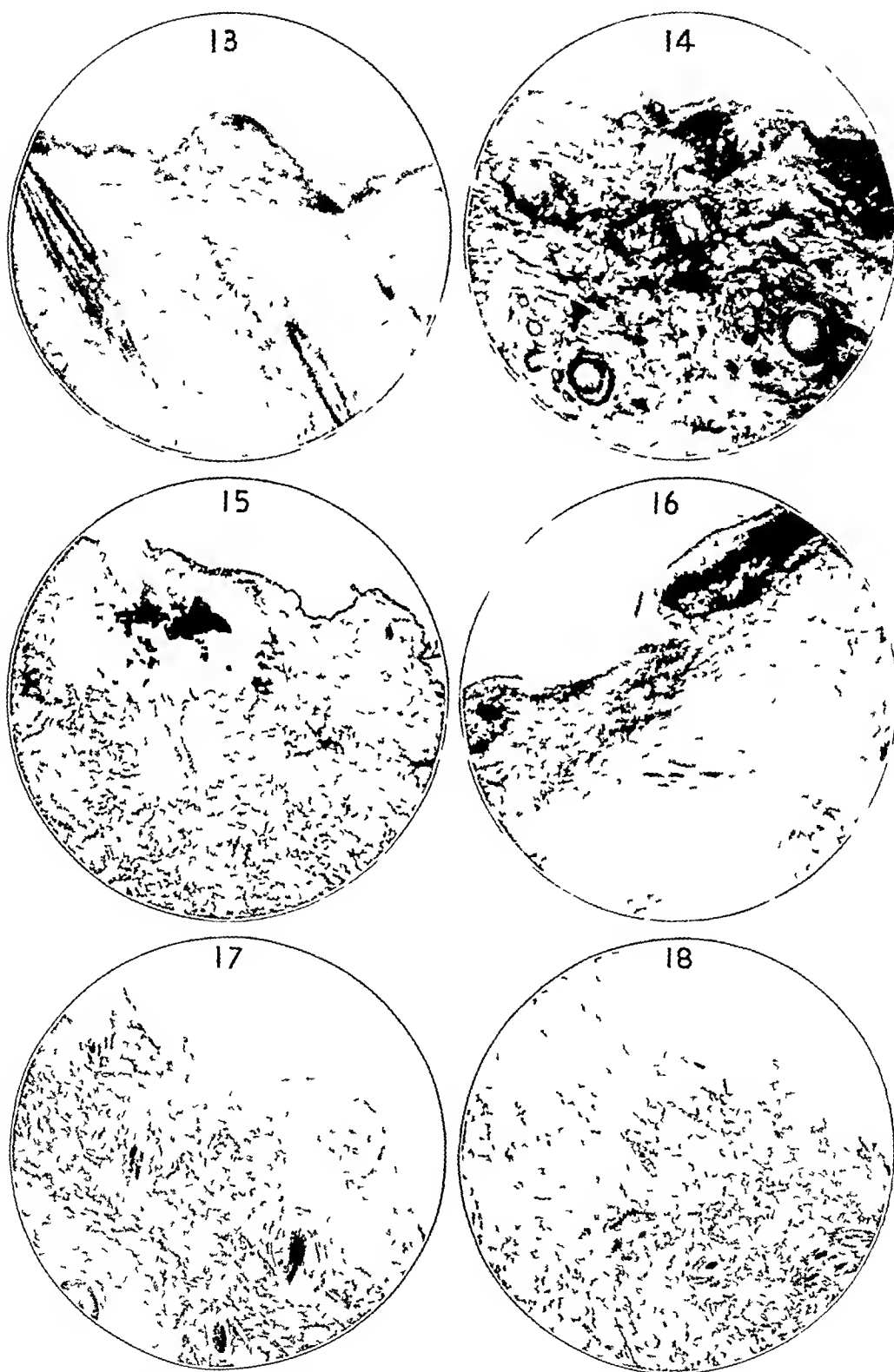
Mustard Burns (Fig 4) The picture is the same as that of the one hour burns except for the presence of more polymorphonuclear leukocytes in the tissue.



Figs 1 to 6—Figure 1 shows a heat burn and figure 2 a mustard gas burn after one hour, figure 3 a heat burn and figure 4 a mustard gas burn after two hours, figure 5 a heat burn and figure 6 a mustard gas burn after three hours (All sections were from stock dogs)



Figs 7 to 12—Figure 7 shows a heat burn of a stock dog after twenty-four hours, figure 8 a mustard gas burn of a stock dog after twenty-four hours, figure 9 a mustard gas burn of Mexican hairless dog 15 after twenty-four hours, figure 10 a heat burn of a stock dog after forty hours, figure 11 a mustard gas burn of a stock dog after forty hours, figure 12 a heat burn of Mexican hairless dog 15 after forty-eight hours.



Figs 13 to 18—Figures 13 and 14 show heat burns after seventy-two hours, figures 15 and 16 mustard gas burns after seventy-two hours, figures 17 and 18 heat burns after ninety-six hours (All sections were from stock dogs)

THREE HOURS—Heat Burns (Fig 5) Fusion of the epithelial cells had occurred, with complete disintegration in some places, and the nuclei were extremely pyknotic. There was necrosis of the corium near the epidermis and considerable leukocytic reaction in this area. Pyknosis of the epithelium of the sebaceous glands was more noticeable than before.

Mustard Burns (Fig 6) The epidermis showed more shrinkage in places and slightly more pyknosis of the nuclei, and there was an increase in leukocytic reaction.

TWENTY-FOUR HOURS—Heat Burns (Fig 7) Pyknosis of all the nuclei was more apparent but not as noticeable as in twenty-four hour mustard burns, the epithelium was broken down in one place with considerable inflammatory reaction. There was no evidence of thrombosis of the capillaries.

Mustard Burns (Fig 8) Pyknosis was more noticeable, there were appreciable fusion of the epithelial cells and much shrinkage of the epithelium.

FORTY HOURS—Heat Burns (Fig 10) Coagulation and fusion of the epithelium were more pronounced, there was necrosis of the corium just next to the epidermis, with inflammatory reaction in this area.

Mustard Burns (Fig 11) Pyknosis of the nuclei of the epidermis was intense in areas where coagulation had not taken place, and small points of inflammatory reaction were observed at scattered intervals under the epidermis.

FORTY-EIGHT HOURS—Heat Burns At this stage the picture was about the same as that of the forty-hour burns.

Mustard Burns Coagulation of the epidermis was more advanced.

SEVENTY-TWO HOURS—Heat Burns (Figs 13 and 14) Complete necrosis of the epithelium and necrotic epithelium desquamated over large areas were observed, as well as considerable purulent reaction in the corium of the denuded areas, both at the surface and deeper in the corium. The nuclei of the capillary walls were intensely pyknotic.

Mustard Burns (Figs 15 and 16) The picture was the same as that of the heat burns except that there was not quite so much pus, though there was a more widespread diffuse inflammation, extending deeper into the corium. The epithelium was necrotic and desquamated. The nuclei of the capillary walls were pyknotic, though not with the same degree of intensity as in the heat burns.

NINETY-SIX HOURS—Heat Burns (Figs 17 and 18) The epithelium was entirely gone in some sections. The denuded corium presented the appearance of the wall of an abscess. There were surface hemorrhage, diffuse leukocytic reaction deep in the corium and pyknosis of the nuclei of all cells.

Mustard Burns (Fig 19) The epithelium was still present in places but hardly recognizable as a cellular structure, coagulation and dissolution being so complete. Where the epithelium was absent, the same picture was presented as in heat burns. Where the epithelium was present, even in a state of dissolution, it seemed to act somewhat as a barrier to infection.

FIVE DAYS—Heat Burns No change was observed from the condition of the ninety-six hour burns except that leukocytosis, both superficial and deep, was increased.

Mustard Burns There was no change from the picture of the ninety-six hour burns except that leukocytosis, both superficial and deep, was increased.

SIX DAYS—Heat Burns (Fig 20) The surface was covered with debris infiltrated with pus. All nuclei

were moderately pyknotic. This stage was merely an extension of the fourth and fifth day processes.

Mustard Burns (Fig 21) This phase was the same as that of the heat burns except that there was more infiltration of pus into the corium and was merely an extension of the fourth and fifth day processes.

SEVEN DAYS—Heat Burns The depth of the surface pus had increased.

Mustard Burns This stage was the same as that of the six day burns.

EIGHT DAYS—Heat Burns (Fig 23) The surface was necrotic, and there were considerable round cell infiltration of the corium, some new fibroblasts and no pyknosis.

Mustard Burns (Fig 24) The surface was covered with purulent debris, deeper and more extensive than before, and the nuclei of the corium were slightly pyknotic.

NINE DAYS—Heat Burns The surface was covered with fibrin and blood, with inflammatory infiltration, and the corium was infiltrated with round cells.

Mustard Burns This phase was the same as that of the heat burns except that there was more pus.

TEN DAYS—Heat Burns The surface was covered with debris and fibrin, under which there was a layer of pus. There was no evidence of regeneration.

Mustard Burns The picture was the same as that of the heat burns except that the pus had infiltrated to a greater extent.

ELEVEN DAYS—Heat Burns (Fig 25) A scab composed of fibrin, blood and pus overlying the ulcer and some regeneration and overgrowth of the epithelium were observed.

Mustard Burns (Fig 26) This phase was the same as that of the heat burns, though there was less regeneration of the epithelium.

TWELVE DAYS—Heat Burns No change was observed.

Mustard Burns (Fig 27) The only change observed was that more regeneration of the epithelium had occurred.

THIRTEEN DAYS—Heat Burns (Fig 30) There was regeneration of the young epithelium under the scab entirely across the ulcer.

Mustard Burns (Fig 31) There was regeneration of the epithelium under the scab, though the ulcer was not bridged across.

FOURTEEN DAYS—Heat Burns No change was observed.

Mustard Burns Further advances of the epithelial growth were noted.

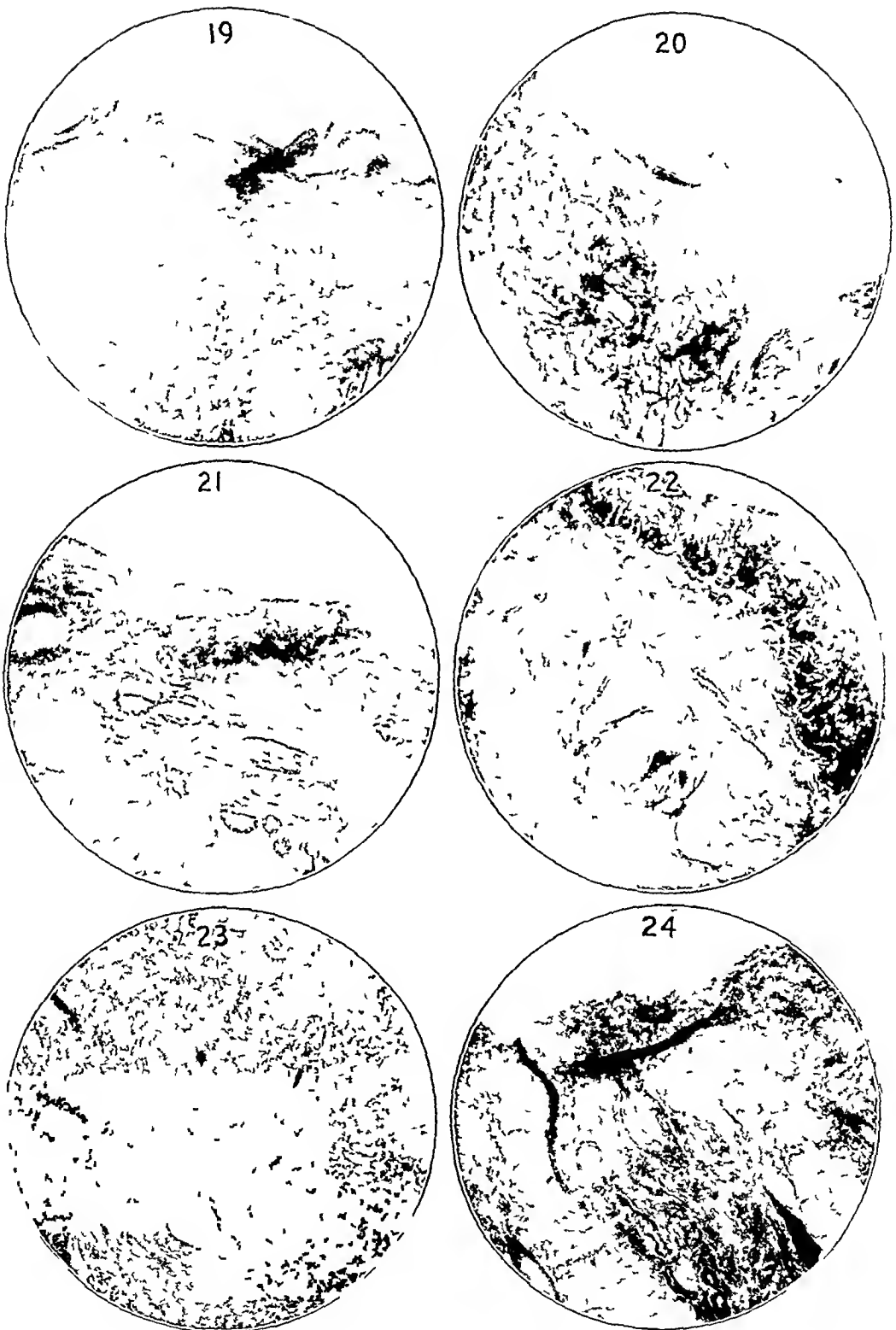
FIFTEEN DAYS (Dog 12)—Heat Burn The surface was still covered with debris, which was lying on newly regenerated epithelium and granulation tissue covered with pus. There was no evidence of pyknosis.

Mustard Burn The surface was covered with debris, which was lying on newly regenerated epithelium and chronic inflammatory tissue, resembling early granulation tissue. The nuclei were slightly pyknotic.

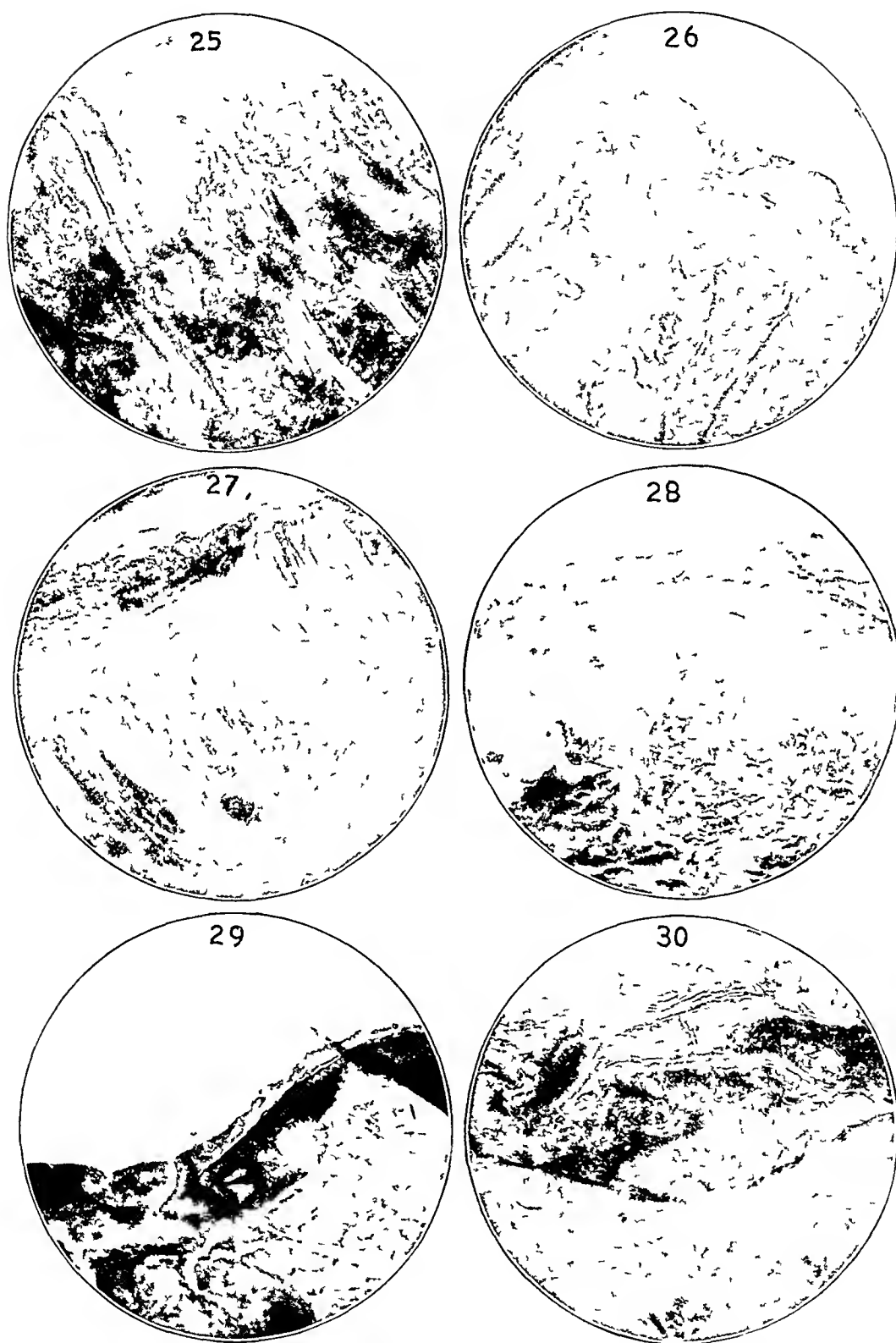
SIXTEEN DAYS—Heat Burns (Fig 32) New epithelium was lying on healthy new corium, and there was no pyknosis.

Mustard Burns (Fig 33) This stage was the same as that of the heat burns except that there was but little new corium, and the new epithelium seemed to be lying for the most part on the old corium. (Had most of the inflammatory tissue sloughed off and the epithelium grown directly across the old corium?)

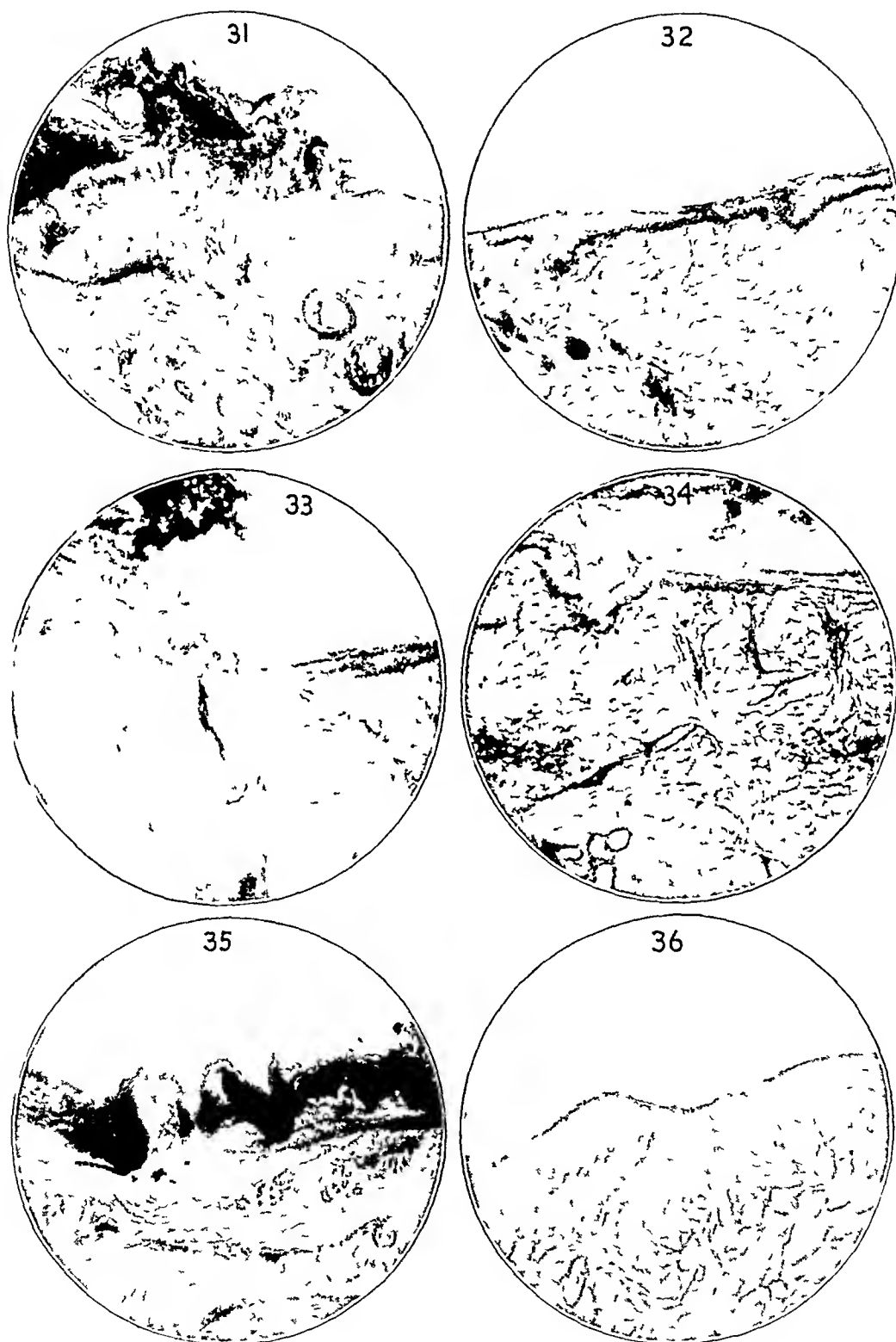
SEVENTEEN DAYS (Dog 13)—Heat Burn No change was observed.



Figs 19 to 24—Figure 19 shows a mustard gas burn of a stock dog after ninety-six hours, figure 20 a heat burn of a stock dog after six days, figure 21 a mustard gas burn of a stock dog after six days, figure 22 a mustard gas burn of Mexican hairless dog 15 after six days, figure 23 a heat burn of a stock dog after eight days, figure 24 a mustard gas burn of a stock dog after eight days



Figs 25 to 30—Figure 25 shows a heat burn of a stock dog after eleven days, figure 26 a mustard gas burn of a stock dog after eleven days, figure 27 a mustard gas burn of a stock dog after twelve days, figure 28 a heat burn of Mexican hairless dog 15 after twelve days, figure 29 a mustard gas burn of Mexican hairless dog 5 after twelve days, figure 30 a heat burn of a stock dog after thirteen days.



Figs 31 to 36—Figure 31 shows a mustard gas burn of a stock dog after thirteen days, figure 32 a heat burn of a stock dog after sixteen days, figure 33 a mustard gas burn of a stock dog after sixteen days, figure 34 a mustard gas burn of Mexican hairless dog 15 after sixteen days, figure 35 a mustard gas burn of a stock dog after nineteen days, figure 36 a heat burn of Mexican hairless dog 18 taken after eighteen days

Mustard Burn There was partial regeneration of the epithelium. The base of the ulcer showed dilated capillaries and cellular debris. No inflammatory reaction or pyknosis of the nuclei was evident.

EIGHTEEN DAYS—Heat Burns The only change noted was that the new corium looked slightly more mature.

Mustard Burns This phase was the same as that on the sixteenth day.

NINETEEN DAYS—Heat Burns No change was observed.

Mustard Burns (Fig 35) New epithelium was noted under the scab, lying on new-looking corium similar to that observed on the slide of specimens taken from dogs sixteen days after occurrence of the heat burns.

TWENTY DAYS (Dog 13)—Heat Burn No change was noted, though the new corium now looked almost as mature as the old.

Mustard Burn The ulcerated area was covered with cellular debris. There was no inflammatory reaction or pyknosis of the nuclei. Some regeneration of the epithelium was observed.

TWENTY-ONE DAYS—Heat Burns (Fig 42) Regenerated epithelium (normal-looking, not thickened and not having prolongations) was lying on a thick layer of new corium.

Mustard Burns Regenerated epithelium (thickened in places) was lying on a thin layer of new corium.

TWENTY-TWO DAYS—Heat Burns No change was noted.

Mustard Burns (Fig 43) No change was observed though there was one area the width of a low power field, where the ulcer was not bridged by epithelium.

TWENTY-THREE DAYS (Dog 14)—Heat Burn The ulcerated area was covered with new epithelium, under which lay young connective tissue consisting of many new fibroblasts. There was no pyknosis.

Mustard Burn This stage was the same as that of the heat burn except that the new epithelium and the connective tissue were not so compact and healthy looking. No pyknosis was observed. On another slide was observed (in the center) a typical chronic ulcer base with leukocytes, round cells and new fibroblasts. No pyknosis was noted.

TWENTY-FOUR DAYS (Dog 14)—Heat Burn This was the same as that at twenty-three days. The epithelium was thicker than normal.

Mustard Burn This stage was the same as that observed in a specimen taken from dog 14 twenty-three days after occurrence of the burn.

TWENTY-FIVE DAYS (Dog 14)—Heat Burn (Fig 46) This stage was the same as that observed twenty-three days after occurrence of the burn. Considerable proliferation of the epithelium at one point with chronic inflammatory tissue under it was observed.

Mustard Burn (Fig 47) This stage was the same as that of the specimen taken from dog 14 twenty-three days after occurrence of the burn.

THIRTY-TWO DAYS (Dog 14)—Heat Burn The slide was not satisfactory.

Mustard Burn (Fig 52) New and thickened epithelium was lying on healthy young connective tissue. The regeneration was complete.

Microscopic Observations on Mexican Hairless Dogs

ONE-HALF HOUR (Dog 15)—Heat Burn The picture was the same as that of one hour burns (ordinary dogs) except that the epithelium was almost completely destroyed and that the nuclei of the sebaceous glands were more pyknotic.

Mustard Burn The cells of the horny layer were somewhat swollen, though there was otherwise no departure from the normal.

ONE HOUR (Dog 15)—Heat Burn This stage was the same as that observed one-half hour after occurrence of the burn.

Mustard Burn This stage was the same as that observed one-half hour after occurrence of the burn.

TWO HOURS (Dog 15)—Heat Burn No change was observed.

Mustard Burn No change was observed.

THREE HOURS (Dog 15)—Heat Burn The picture was the same, except for slight leukocytic reaction, as that of the burn two hours after occurrence.

Mustard Burn The epithelium was more swollen.

FOUR HOURS (Dog 15)—Heat Burn No change was observed.

Mustard Burn No change was observed.

TWENTY-FOUR HOURS (Dog 15)—Heat Burn There was appreciable inflammatory reaction, which was more evident than that in the stock dogs.

Mustard Burn (Fig 9) The epithelium was losing its cellular character and was separating. There were inflammatory reaction and hemorrhage under it, which were more noticeable than those in the stock dogs.

FORTY-EIGHT HOURS (Dog 15)—Heat Burn (Fig 12) Inflammatory reaction and hemorrhage were observed.

Mustard Burn No change was noted.

SEVENTY-TWO HOURS (Dog 15)—Heat Burn There was inflammatory reaction of the surface. The changes were not as pronounced as those in stock dogs.

Mustard Burn The epithelium was breaking up, with pus under the necrotic pieces. Surface hemorrhage and leukocytic reaction extending deep in the corium were noted, which were more noticeable than those in the stock dogs.

NINETY-SIX HOURS (Dog 15)—Heat Burn No change was observed.

Mustard Burn No change was observed.

SIX DAYS (Dog 15)—Heat Burn There was superficial inflammatory reaction, and pyknosis of all the nuclei except those of sebaceous glands was observed.

Mustard Burn (Fig 22) Superficial inflammatory reaction and surface hemorrhage were noted. The epithelium was entirely gone. There was pyknosis of all the nuclei except those of the sebaceous glands.

SEVEN DAYS (Dog 17)—Heat Burn Superficial hemorrhage was observed.

Mustard Burn Superficial hemorrhage and subacute inflammatory reaction (small round cells with pyknotic nuclei) were noted.

TEN DAYS (Dog 17)—Heat Burn A thick layer of fibrin, under which there was a layer of pus, with inflammatory reaction in adjacent tissues, was present.

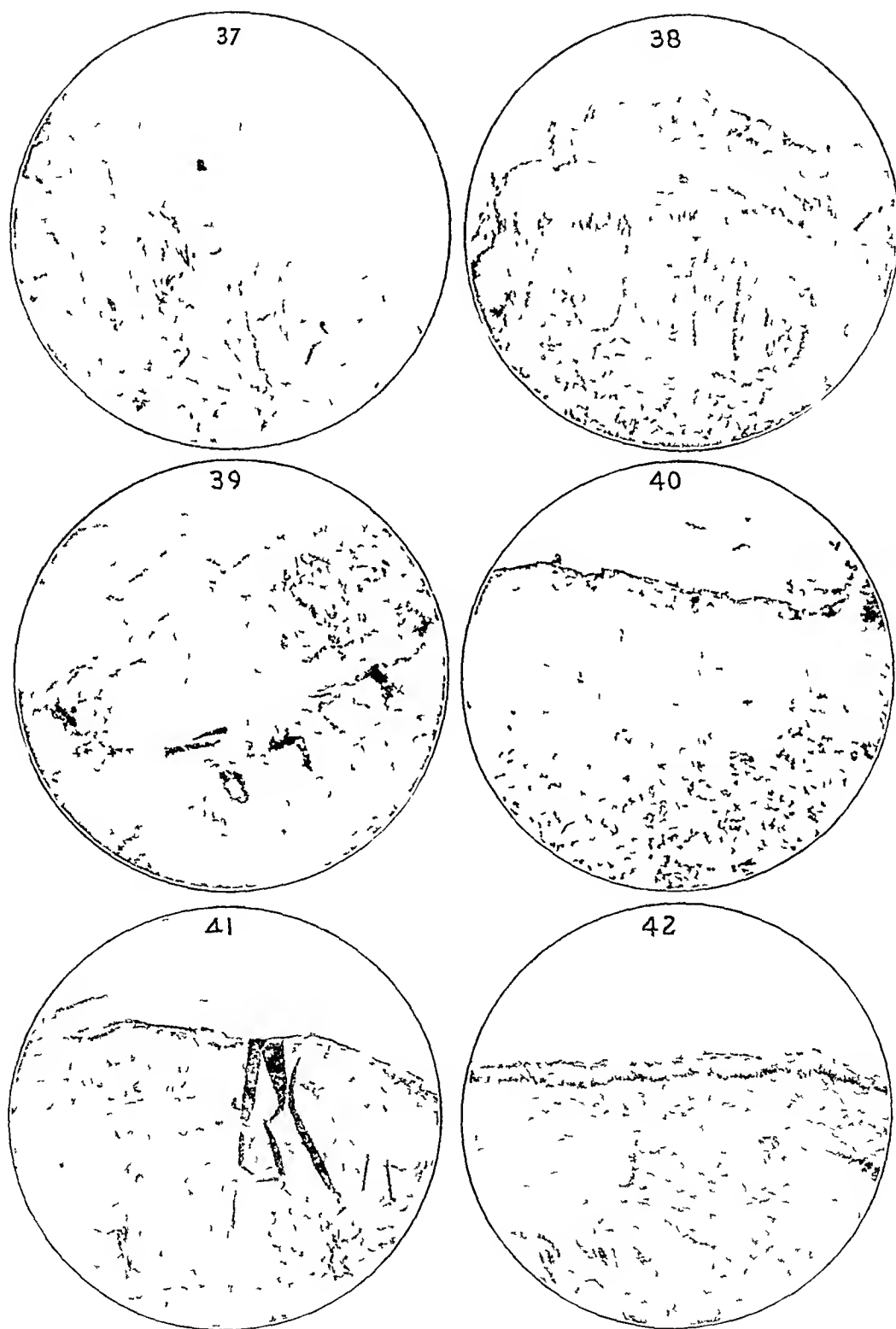
Mustard Burn Exactly the same type of reaction as that in the heat burn was observed.

TWELVE DAYS (Dog 15)—Heat Burn (Fig 28) The wound showed no inflammatory reaction. There was regeneration of the epithelium at the edges.

Mustard Burn (Fig 29) The wound showed little inflammatory reaction. Regeneration of the epithelium at the edges was noted.

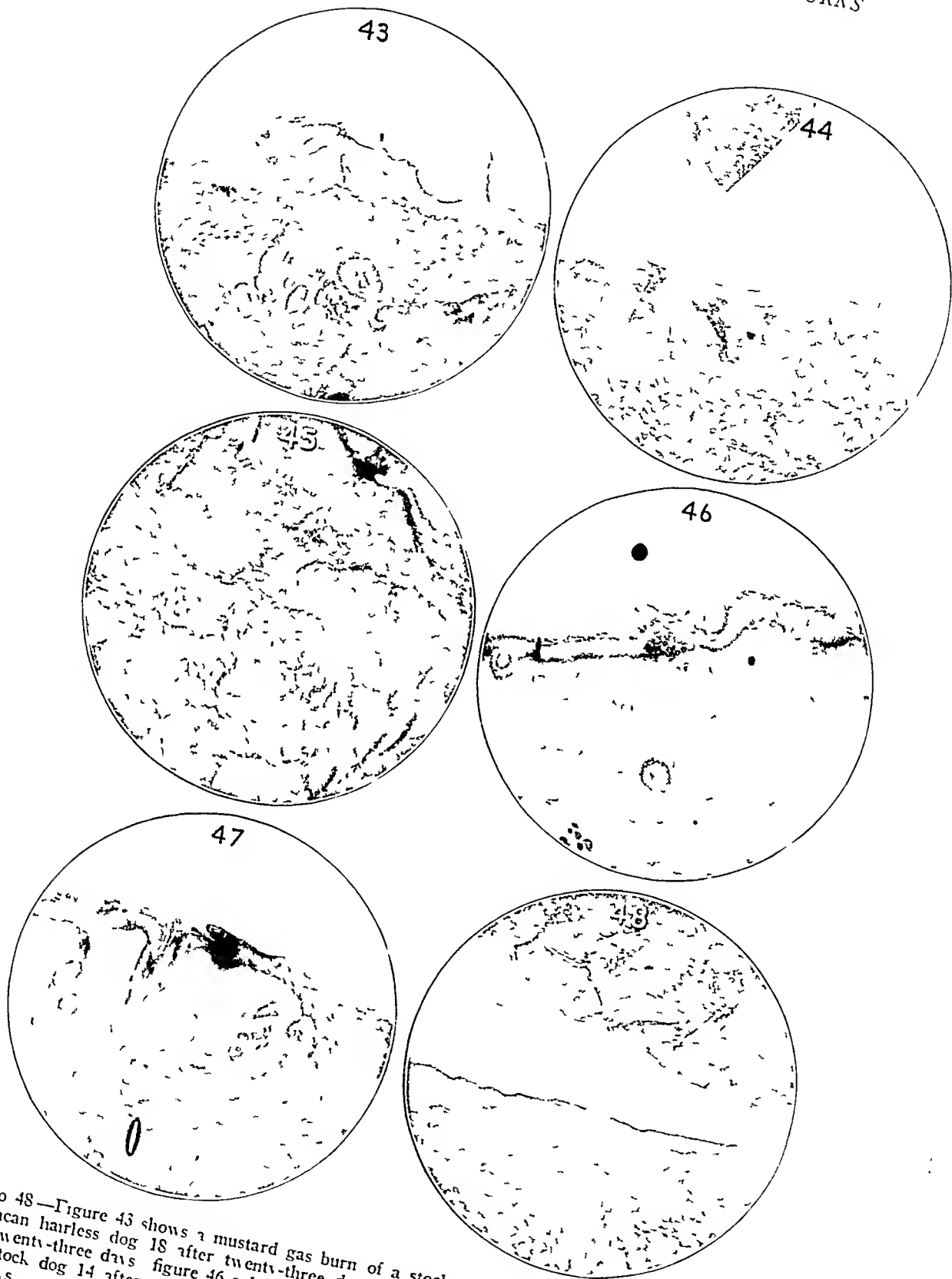
FOURTEEN DAYS (Dog 17)—Heat Burn The reactions were the same as those observed ten days after occurrence of the burn except that the pus was more attenuated.

Mustard Burn The picture was the same as that of the heat burn though the inflammatory reaction had subsided far more.



Figs 37 to 42—Figure 37 shows a mustard gas burn of Mexican hairless dog 18 after eighteen days, figure 38 a heat burn of Mexican hairless dog 18 after twenty days, figure 39 a mustard gas burn of Mexican hairless dog 18 after twenty days, figure 40 a heat burn of Mexican hairless dog 16 after twenty days, figure 41 a mustard gas burn of Mexican hairless dog 16 after twenty days, figure 42 a heat burn of a stock dog after twenty-one days

KOONTZ—HEAT AND MUSTARD GAS BURNS



Figs 43 to 48—Figure 43 shows a mustard gas burn of a stock dog after twenty three days, figure 44 a heat burn of Mexican hairless dog 18 after twenty-three days, figure 45 a mustard gas burn of Mexican hairless dog 18 after twenty-three days, figure 46 a heat burn of stock dog 14 after twenty-five days, figure 47 a mustard gas burn of stock dog 14 after twenty-five days, figure 48 a heat burn of Mexican hairless dog 18 taken after twenty-five days

SIXTEEN DAYS (Dog 15)—Heat Burn No change was observed

Mustard Burn (Fig 34) The wound was almost entirely epithelized under a scab

SIXTEEN DAYS (Dog 17)—Heat Burn A thick layer of fibrin with a small amount of pus adherent to the under surface was observed

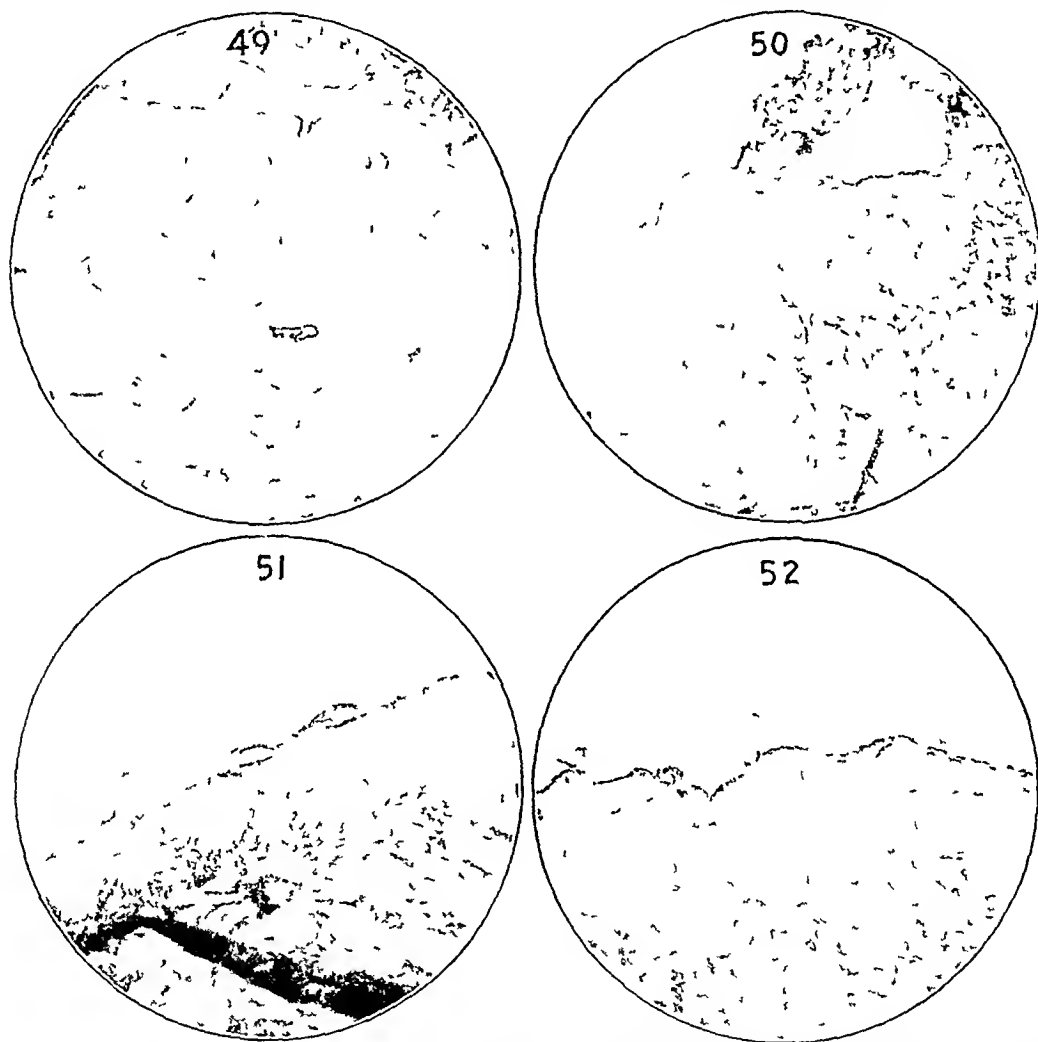
Mustard Burn There was regeneration of the epithelium in places A mild superficial inflammatory reaction was noted where the epithelium was not regenerated The ulcerated area was clean

EIGHTEEN DAYS (Dog 16)—Heat Burn Inflammatory reaction extended deep into the corium in some

TWENTY DAYS (Dog 16)—Heat Burn (Fig 40) Regeneration of hypertrophied epithelium, lying on new corium, was observed

Mustard Burn (Fig 41) The picture was the same as that of the heat burn except that the hypertrophy took the form of thickness rather than that of prolongation of epithelium growing into the corium Also, there was less new corium

TWENTY DAYS (Dog 18)—Heat Burn (Fig 38) The epithelium was completely regenerated under the scab and was greatly hypertrophied, being on a base of healthy-looking granulation tissue



Figs 49 to 52—Figure 49 shows a mustard gas burn of Mexican hairless dog 18 after twenty-five days, figure 50 a heat burn of Mexican hairless dog 18 after thirty days, figure 51 a mustard gas burn of Mexican hairless dog 18 after thirty days, figure 52 a mustard gas burn of stock dog 14 after thirty-two days

places There was regeneration of epithelium lying on new corium in other places

Mustard Burn Partial regeneration of the epithelium with little new corium was observed

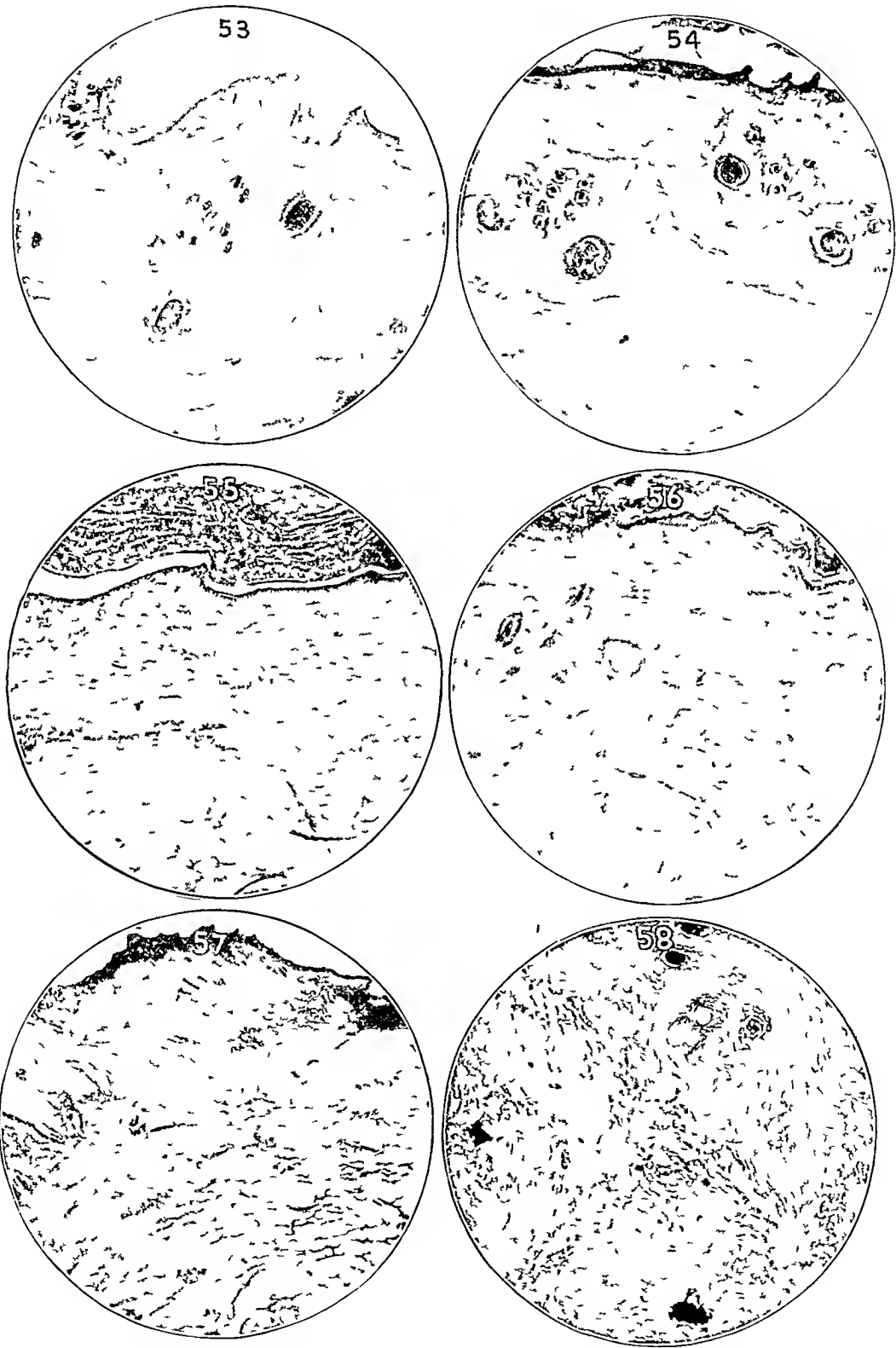
EIGHTEEN DAYS (Dog 18)—Heat Burn (Fig 36) New epithelium lying on new corium was of approximately the same maturity as that in other eighteen day burns There was no pyknosis

Mustard Burn (Fig 37) The floor of the ulcer was clean except for slight inflammatory reaction The scab was still present in some slides where the epithelium was regenerated to about the same degree as that in heat burns

Mustard Burn (Fig 39) The surface of the wound was covered with blood, fibrin and pus (scab) There was no granulation tissue Regeneration of the epithelium at the edges under the scab was noted

TWENTY-THREE DAYS (Dog 18)—Heat Burn (Fig 44) There was regeneration of the epithelium in the middle of the burned area An overlay of blood, fibrin and pus was observed

Mustard Burn (Fig 45) Regeneration of the hypertrophied epithelium on healthy granulations except in middle of the burned area was noted There was an overlay of scab composed of blood, pus and fibrin



Figs 53 to 58—Sections of burned and of normal skin of goats injected with india ink

TWENTY-FOUR DAYS (Dog 18)—Heat Burn No change was observed

Mustard Burn There was no change

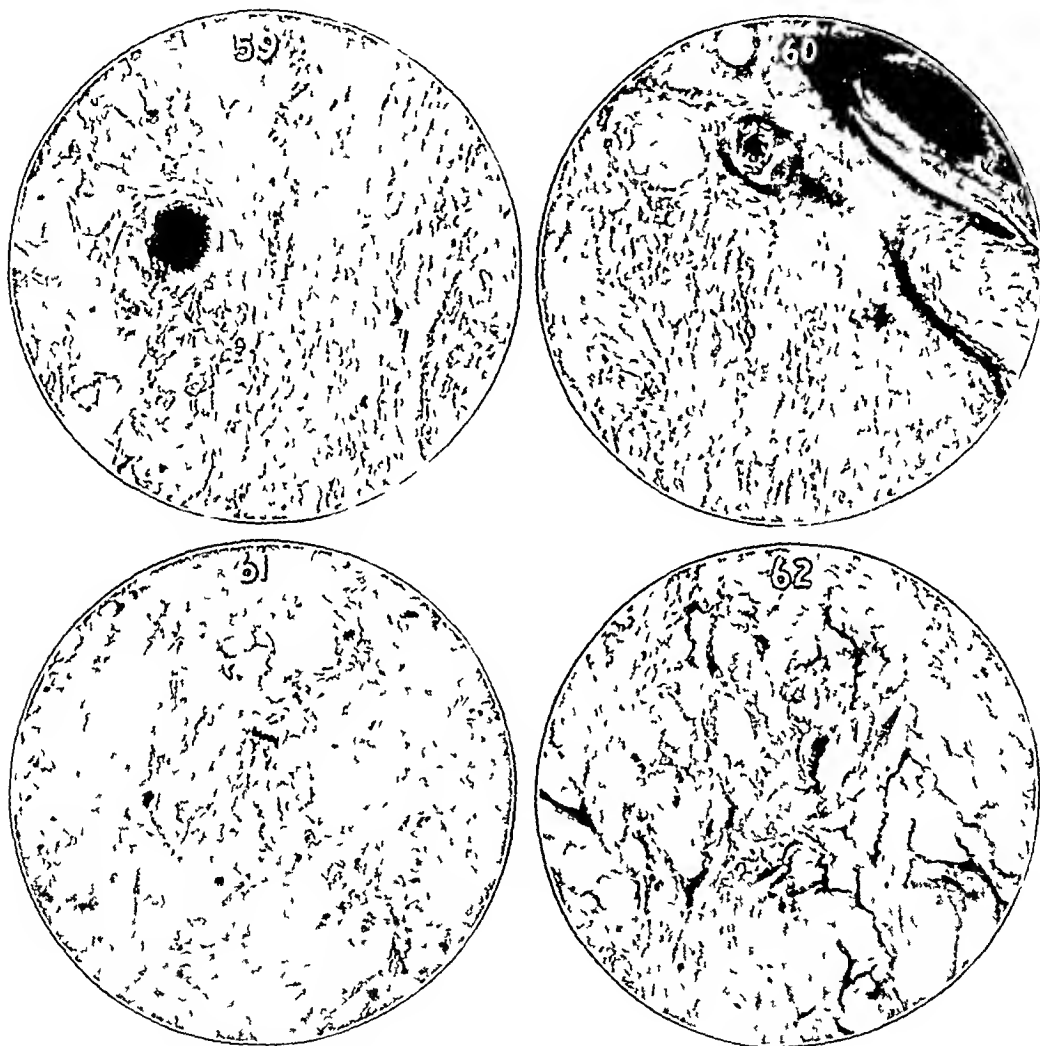
TWENTY-FIVE DAYS (Dog 18)—Heat Burn (Fig 48) There was regeneration of the epithelium except in the middle of the burned area. Healthy young connective tissue was present under the epithelium. There was an overlay of scab of blood, fibrin and pus. No pyknosis was observed.

Mustard Burn (Fig 49) The picture was the same as that of the heat burn except that the layer of con-

Mustard Burn The pathologic process was the same as that of the heat burn.

THIRTY DAYS (Dog 18)—Heat Burn (Fig 50) The healing process was not as complete as that in the dog observed twenty-seven days after occurrence of the burn. A slide with a specimen from another dog showed almost complete healing of the burned area.

Mustard Burn (Fig 51) The healing process was complete, and the epithelium was hypertrophied, a thick layer of rather dense new connective tissue being under it. There was no pyknosis. A slide of a specimen



Figs 59 to 62—Sections of burned and of normal skin of goats injected with India ink

nective tissue under the new epithelium was much thinner. No pyknosis was noted.

TWENTY-SIX DAYS (Dog 16)—Heat Burn The picture was the same as that of the heat burn of the dog observed twenty-five days after occurrence of the burn except that regeneration of the epithelium was complete.

Mustard Burn The picture was the same as that of the burn of the dog observed twenty-five days after occurrence of the burn except that regeneration of the epithelium was complete.

TWENTY-SEVEN DAYS (Dog 18)—Heat Burn The pathologic factors were the same as those of the burn of the dog observed twenty-five days after occurrence of the burn except that healing in the center of the burned area was more nearly complete. The new epithelium was hypertrophied.

from the burned area of another dog showed a gap not epithelized which was slightly wider than a low power field.

II EXPERIMENTS WITH GOATS TO DETERMINE THE RELATIVE AMOUNT OF CAPILLARY THROMBOSIS IN HEAT BURNS AND MUSTARD BURNS

In this series of tests 11 goats which had heat and mustard burns of various ages (the short periods, twenty-four and forty-eight hours, being used principally) were given injections of India ink in order to determine the relative amount of thrombosis in the capillaries of the two burn areas. The India ink was injected into the

jugular vein, so as to get it into the general circulation and to make the possibilities of its reaching the various parts of the skin the same for all parts of the body. Specimens of the normal skin area were taken for microscopic examinations, as well as material from each of the burns on each goat. There was difficulty in some cases in getting the ink to enter the capillaries of the skin, possibly because of some mechanical property of the suspension. But when the ink did enter the capillaries, it entered those of the normal skin and those of the areas burned by heat and by mustard gas in about equal degrees, as is shown in figure 53 to 62. This seems to indicate that there was no thrombosis of the capillaries, because, if thrombosis were present, the ink could not have entered them.

III EXPERIMENTS WITH GOATS TO DETERMINE THE EXTENT OF THE INFLAMMATORY AREA BEYOND THE POINT OF APPLICATION IN HEAT BURNS AND IN MUSTARD BURNS

Several goats with heat and mustard gas burns on their skins were given intravenous injections of trypan blue in order to determine the extent of the inflammatory reaction beyond the actual burned area. Menkin⁶ had previously shown that trypan blue injected intravenously stained inflamed tissues deeply but passed through normal tissues, leaving them entirely unstained. In these experiments it was observed that the stained areas about the mustard burns were about twice the size of those about the heat burns, and this showed that the inflammatory reaction extended farther beyond the burned areas in the case of mustard gas burns than in the case of heat burns.

IV EXPERIMENTS WITH RABBITS TO DETERMINE THE RELATIVE HEALING TIME OF MUSTARD BURNS AND OF HEAT BURNS

Heat and mustard burns, as nearly equal in intensity as possible, were made on the skins of rabbits, and they were photographed from time to time in order to show the progress in healing of the two types of burns. A number of rabbits were used, and little difference could be detected in healing time.

⁶ Menkin, V. Studies on Defflamation. I. Fixation of Vital Dyes in Deffamed Areas, *J. Exper. Med.* 50: 171-180, 1929.

COMMENT

These experiments show minor, not pronounced and apparently not fundamental differences between heat burns and mustard burns. Warthin and Weller's observation as to the greater moistness of the affected area of mustard burns is correct. So far as I have been able to determine, the condition of the vessels in the two types of burns is the same. The leukocytic reaction in mustard burns is not so slight as Warthin and Weller's observations indicate. This reaction is more diffuse than the reaction in heat burns and extends farther into the corium. In heat burns, the reaction tends more toward a walling-off process, as in abscesses. Naturally, all burns in these series of experiments were infected—a condition which presented a uniformly complicating factor. Little difference could be made out in the pyknosis of the nuclei in the two types of burns.

From the practical point of view, the healing period is by far the most important period in either type of burn. There is little difference in the healing stages, either from the point of view of time or from the nature of the scars. The epithelium is hypertrophied in both instances. In the case of heat burns, the hypertrophy is apt to take the form of prolongations of epithelium into the corium, and in mustard burns, to take the form of fairly uniform thickening. Also, in the case of heat burns there seems to be more tendency to formation of granulation tissue, so that the new epithelium, when the wound heals, lies on a thicker layer of new corium than that on which the new epithelium lies in mustard burns.

Probably the most important result of this investigation is the demonstration of the fact that the healing time of heat burns and that of mustard burns of equal intensity are practically the same. (All of these burns were, of course, entirely untreated.) This seems to indicate that the same treatment is applicable to both types of burns.

CONCLUSIONS

So far as the experimental results herein reported are concerned, there is justification for drawing the conclusion that there is no major difference, either qualitative or quantitative between heat burns and mustard burns of equal intensity. The healing times of the two types of burns are practically the same.

UNTOWARD EFFECTS OF VARIOUS SUBSTANCES RECOMMENDED FOR BURNS OR WOUNDS

EXPERIMENTAL TESTS ON RATS

ROGER D BAKER, M D

DURHAM, N C

Many substances have been recommended for application to burns¹ and wounds, either as dressings or detergents. Some of these have been subjected to testing in rats, and the results are herewith presented.

Testing of substances for local effect on human beings under controlled conditions may be satisfactory and harmless, as shown by Cannon and Cope,² who applied tannic acid and methylosaniline chloride (gentian violet) to donor sites from which skin had been removed for grafting, and compared the rates of healing with those of a control area. Spontaneous human burns and wounds vary so greatly in size, depth, location and cleanliness that they cannot be used as standardized lesions to judge therapeutic results.

A method has been devised utilizing an inexpensive laboratory animal, the rat, which indicates the necrotizing effect locally in a quantitative fashion, and which permits some conclusions to be drawn regarding the general effects resulting from absorption of the material to be tested.

A previous report by Handler and me has been published³ in which essentially this method was used in studies on tannic acid. From them it was learned, for instance, that hepatic necrosis could be produced by applying tannic acid in either ointment or aqueous form to the area denuded of skin, if the area was large enough. Extensive studies have been reported recently by Hartman and Romence,⁴ who used dogs to test

particularly damage to the liver resulting from various agents which have been used on burns.

Adult white rats are anesthetized with ether and the skin of the abdomen and thorax is removed over an area 8 by 10 cm. The material to be tested is then applied to this skinned area for a standard period of time (three minutes in the following experiments) by means of gentle swabbing with cotton pledgets. The rats are not bandaged. Their behavior after the application is observed. They are killed at the end of

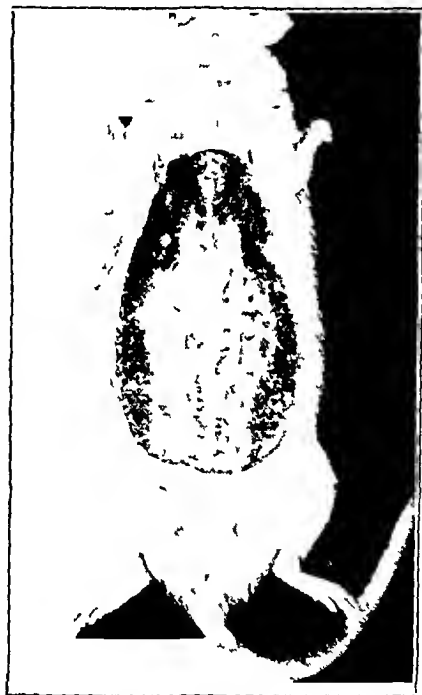


Fig 1—Size of area of skin removed from rats to make the tests reported in table 1. The muscle of the abdominal wall lies exposed, but a transparent layer of connective tissue overlies the muscle.

From the Department of Pathology, Duke University School of Medicine and Duke Hospital.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University.

1 Harkins, H N. *The Treatment of Burns*, Springfield, Ill., Charles C Thomas, Publisher, 1942.

2 Cannon, B, and Cope, O. *Rate of Epithelial Regeneration. Clinical Method of Measurement, and Effect of Various Agents Recommended in Treatment of Burns*, Ann Surg **117** 85-92 (Jan) 1943.

3 Baker, R D, and Handler, P. *Animal Experiments with Tannic Acid Suggested by the Tannic Acid Treatment of Burns*, Ann Surg **118** 417-426 (Sept) 1943.

4 Hartman, F W, and Romence, H L. *Liver Necrosis in Burns*, Ann Surg **118** 402-416 (Sept) 1943.

twenty-four and forty-eight hours, autopsy is performed, and the treated abdominal wall, heart, lungs, liver, spleen and kidneys are taken for histologic examination. The time intervals selected are those at which histologically demonstrable damage becomes manifest and before changes due to bacterial contamination are important. In addition the stage of healing or repair has not begun to any appreciable extent.

The method, as used, indicates the direct necrotizing effect of the substance applied and also the generalized acute effects as indicated by death of the rat, abnormal behavior of the

In those instances in which the depth of necrosis is given as zero there was no necrosis of muscle in any animal. When necrosis was present it

TABLE 1—Necrotizing Local Effect and Some Generalized Effects from Application of Various Substances to Rat's Abdominal Wall Denuded of Skin*

	Depth of Necrosis No. of Muscle Fiber Layers, Average	Comment
Nothing applied	0	
Isotonic solution of sodium chloride	0	
Boric acid ointment (U S P)	0	
Petrolatum (U S P)	0	
Motor oil (Esso no 3)	0	
Benzene	0.5	Muscular tremors for 30 minutes
Ether	0.5	Bleeding and reddening of treated area
White soap (Ivory)	0.5	
Hexylresorcinol	2.0	
Medicinal soft soap U S P (50% aqueous)	2.0	
Alcohol 95%	3.0	Three died
Solution of hydrogen peroxide U S P (50% aqueous dilution)	3.5	Application for 30 seconds only 3 minutes caused death
Tannic acid 10%	6.0	Hepatic necrosis, central, in 4
Silver nitrate 10%	9.0	

* Each substance was tested on 6 rats

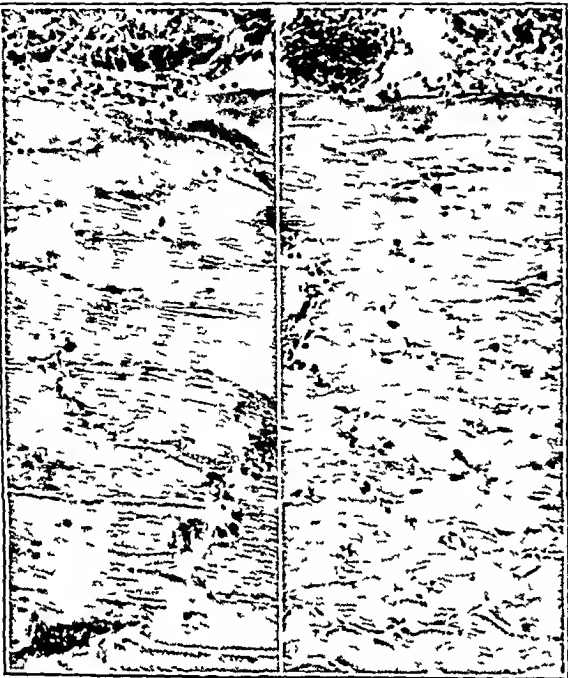


Fig 2—Left Microscopic section from abdominal wall of rat in area denuded of skin and treated with isotonic solution of sodium chloride. The muscle remains normal and the overlying connective tissue persists. All sections taken twenty-four or forty-eight hours after application of test substances. Right After application of petrolatum. Same result as from isotonic solution of sodium chloride.

rat or histologic changes in the more important viscera. If the effect of substances on rate of healing, or long time toxic effects, were to be studied the experimental procedures would need appropriate modification.

Study of skinned abdominal walls of rats which are untreated or treated with isotonic solution of sodium chloride indicates that a thin layer of connective tissue remains overlying the muscle of the abdominal wall. After an animal is thus skinned, substances with much necrotizing effect penetrate this thin connective tissue layer and cause necrosis of the abdominal muscle. The degree of necrotizing effect can then be expressed by counting the number of layers of necrotic muscle fibers, observed microscopically. The muscle mass of the abdominal wall of the rats used averaged 40 muscle fiber layers, but varied in thickness from 31 to 58.

Table 1 gives the results. Six rats were used for each substance, killed at twenty-four or at forty-eight hours after the applications. The results were essentially the same whether examination was made after twenty-four or forty-eight hours

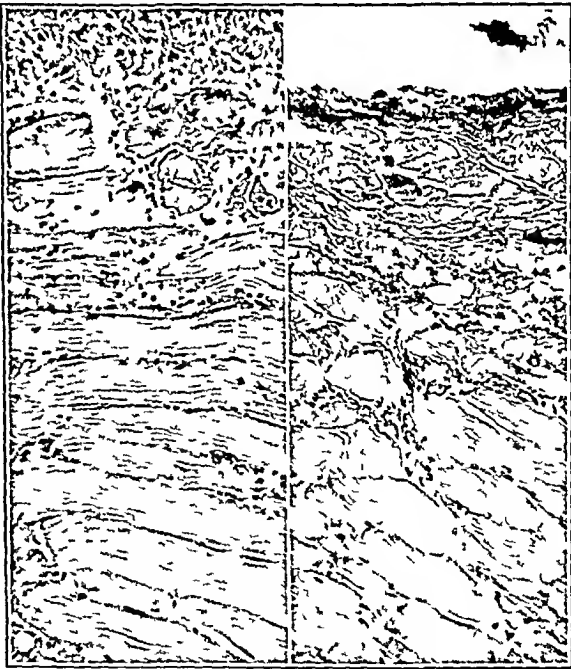


Fig 3—Left Effect of medicinal soft soap U S P (50 per cent aqueous). The two superficial layers of muscle fibers are necrotic, as shown by hyaline and vacuolar change and interruption of continuity of fibers. There is inflammatory reaction among necrotic fragments. The overlying connective tissue layer remains. Right Effect of solution of hydrogen peroxide U S P diluted to half strength with water. Necrosis, indicated by hyaline muscle fibers, extends to a depth of about six layers, deeper in this instance than the average noted in the 6 rats tested. The overlying connective tissue has been destroyed.

varied from rat to rat and occurred to varying depths in different parts of the section from the abdominal wall of the same rat For example, the six rats treated with medicinal soft soap U S P (green soap) showed necrosis to a depth of 1, 2.5, 1, 2, 3 and 2.5 muscle fiber layers respectively Likewise, the six rats treated with ether showed necrosis to a depth of 0.5, 0.25, 0.1, 0, 1 and 2 muscle fiber layers respectively

Death occurred spontaneously only in those rats treated with 95 per cent alcohol Instead of recovering promptly from the ether anesthesia, these rats remained stuporous for several hours or until death, and it is supposed that the absorption of alcohol was sufficient to cause death Alcohol levels in the blood were determined by Dr Haywood Taylor in 6 additional rats, 3 treated with 95 per cent alcohol and 3 with isotonic solution of sodium chloride, and

TABLE 2—*Alcohol Content of Blood from (a) Rats Treated with 95 Per cent Alcohol Over Area Denuded of Skin as Compared with (b) Rats Treated with Isotonic Solution of Sodium Chloride Over Similar Areas*

Rats treated with alcohol	530.1 mg	per 100 cc
	369.9 mg	per 100 cc
	441.4 mg	per 100 cc
Average	447.1 mg	per 100 cc
Rats treated with saline solution	29.9 mg	per 100 cc
	21.2 mg	per 100 cc
	12.8 mg	per 100 cc
Average	21.3 mg	per 100 cc

* The figures indicate the high absorption of alcohol into the blood stream from body surfaces denuded of skin

samples of blood were taken two hours after application of the substance

The figures in table 2 indicate the great absorption of alcohol into the blood stream from areas denuded of skin

In addition to the muscular tremors of the animals treated with benzene, it was noted that rats placed in a closed container could be readily killed by the fumes of benzene, and would sometimes die if treated in a shallow pan

The fatal effect of application of 50 per cent solution of hydrogen peroxide U S P (i e., solution of hydrogen peroxide U S P diluted with an equal amount of water) to the skinned area for the full three minute period was corroborated in 6 additional rats, and dissection of the thoracic organs indicated that death was due to air embolism Application to smaller areas, one-half or one-quarter as large, did not cause death In Cushny's "Pharmacology and Thera-

peutics," it is stated that "the formation of emboli is seen most frequently in the rabbit, but was in all probability the cause of death in one case of fatal poisoning in man, in which a solution of hydrogen peroxide had been used to wash out the pleural cavity Emboli are not formed in the dog on hypodermic injection"

No change in the internal organs could be attributed to any of the substances used except the hepatic necrosis produced when tannic acid was applied

The necrosis of muscle at the site of application appeared to be due to the direct effect of the substance applied and not to overlying bacterial growth, since bacterial growth was superficial and was observed in the controls and in connection with substances which produced no necrosis of muscle

REMOVAL OF PETROLATUM BY DETERGENTS

A series of experiments was carried out in which petrolatum was applied to the denuded area, allowed to remain for a time and then removed by various methods recommended in the literature for the removal of grease and oils from burns, following first aid or home treatment of burns and prior to definitive hospital treatment Some of the methods suggested were as follows

- 1 Wash with warm water and ether
- 2 Use a mixture of medicinal soft soap U S P and solution of hydrogen peroxide followed by hexylresorcinol
- 3 Wash for ten minutes with soap and water or isotonic solution of sodium chloride
- 4 Use ether or benzene followed by copious flushing with isotonic solution of sodium chloride
- 5 Use 50 per cent medicinal soft soap (aqueous solution, not tincture) and a 50 per cent dilution of solution of hydrogen peroxide U S P

The experimental animals were subjected to these treatments to remove the petrolatum These substances removed the petrolatum with varying degrees of efficiency, but in so doing exerted the same untoward effects which have already been shown It is to be realized, of course, that the experimental lesions were not burns but wounds and that the surface of a deep burn usually has a layer of necrotic tissue to begin with, as a result of the burn itself

TANNIC ACID VERSUS TANNIC ACID-SILVER NITRATE

The same experimental method was used to compare the relative hazards of the tannic acid-silver nitrate treatment of burns and the tannic acid treatment of burns To be determined were (1) the degree of hepatic damage and

5 Edmunds, C W, and Gunn, J A Cushny's Pharmacology and Therapeutics, ed 12, Philadelphia, Lea & Febiger, 1940, p 790

(2) the degree of necrotizing effect at the site of application. The tannic acid-silver nitrate combination was applied to 36 rats according to the following method. A freshly prepared aqueous solution of tannic acid was sprayed over the denuded area. This was followed immediately by spraying the area with a fresh mixture of equal parts of the aqueous tannic acid and 10 per cent silver nitrate solutions. This mixture was then sprayed on the denuded surface every ten minutes for a total of four applications. Tannic acid alone was applied for comparison to 36 more rats. This was applied by spray for a total of 5 applications exactly to duplicate the scheme of application of the tannic acid-silver nitrate mixture. The concentration of silver nitrate was

solutions were used, while such damage was usually present when the tannic acid alone was used. Some damage was produced when concentrations of tannic acid as high as 20 per cent were used in combination with silver nitrate.

Of the 36 rats treated with tannic acid-silver nitrate none had died before the termination of the experiment at forty-eight hours, while of the 36 rats treated with tannic acid alone 10 rats had died before the end of that period.

Sections of the area of application of the test substances indicated that the combination of tannic acid and silver nitrate was essentially as damaging to the muscle of the rat's abdominal wall as the tannic acid, the combination producing necrosis of eight layers of muscle fibers and the tannic acid alone necrosis of nine layers of muscle fibers. The escharotic effect was exhibited to the same degree whether the concentrations used were 10, 15 or 20 per cent.

Thus the silver nitrate-tannic acid treatment appeared to be superior to the tannic acid treatment in rats, with respect to hepatic damage and to mortality, but there was no difference with respect to the local necrotizing effect.

TRIPLE DYE

Similarly "triple dye," frequently used in the treatment of burns, was subjected to experimental analysis. Aqueous triple dye solution (1.5 per cent methylrosaniline chloride, tetraethyl-diaminotriphenylmethane sulfate [brilliant green] and 0.75 per cent acriflavine) was swabbed on the area denuded of skin. Three or four applications were made in a few minutes, with drying allowed between the applications.

Of 10 rats treated with triple dye 7 died before the end of forty-eight hours, while of 10 control rats treated with isotonic solution of sodium chloride none died. In neither group were visceral changes noted microscopically. The animals treated with triple dye were stuporous in comparison with those treated with the isotonic solution of sodium chloride. Necrosis of muscle where the dye was applied occurred to an average depth of 8.5 muscle fiber layers, while there was no necrosis of the muscle in the rats treated with the sodium chloride.

To test further the question of the generalized toxic effect of triple dye, subcutaneous inoculations of the dye were made. Ten rats withstood 2 cc. Of 3 rats receiving 1, 2, and 4 cc respectively, the one receiving the 4 cc died. The area of subcutaneous inoculation showed massive edema and necrosis microscopically.

Various experiments were performed to determine whether the rats treated over the skinned areas may have absorbed dye by licking the



Fig 4—*Left* Effect of 10 per cent tannic acid. Necrosis extends to a depth of six layers of muscle fibers, the average noted in 6 rats. The overlying connective tissue is necrotic. *Right* Effect of 10 per cent silver nitrate. Necrosis extends to a depth of about twelve layers of muscle fibers, deeper than the average noted. The outer half of necrotic muscle is blackened by the silver nitrate. The most superficial fibers are muscle, and the overlying connective tissue has come away.

kept at 10 per cent in all experiments, but that of tannic acid was 10 per cent, 15 per cent, and 20 per cent in the mixture in each dozen animals and in the control groups. Abdominal areas one eighth to one fourth of the total body surface were denuded of skin and treated by the tannic acid-silver nitrate method, by spray, and by the tannic acid alone in the controls.

Damage to the liver was usually absent histologically when the tannic acid-silver nitrate

treated area or whether the stuporous rats failed to take sufficient water to maintain body fluids. These experiments were not conclusive for one reason or another.

The definite conclusion was that triple dye exerted a considerable necrotizing effect locally. While there was some evidence to suggest that triple dye had a deleterious general effect, further evidence was needed before a conclusion could be drawn.

COMMENT

The experimental results show some of the effects on rats following the use of substances which have been applied to large burns or to wounds in human beings. These results indicate that several substances have a necrotizing effect on raw muscle surfaces. Whether this necrotizing effect is sufficient to constitute a contraindication to their use in a human being will depend on the circumstances in the case. In order to avoid this necrotizing effect on muscle, and probably on most other subepidermal tissues, nothing should be applied, or else such substances as isotonic solution of sodium chloride, petrolatum or boric acid ointment should be used. If it is necessary to cleanse the area with substances other than isotonic solution of sodium chloride a substance with slight necrotizing effect should be employed. Of the three substances with the same slight necrotizing effect white soap would appear to be preferable, since ether produced bleeding and reddening of the treated area and there is also the not unimportant danger of inflammability. Benzene, because of toxicity when absorbed from the surface area and by inhalation, is less desirable. The greater necrotizing effect of such substances as hexylresorcinol, medicinal soft soap, alcohol and solution of hydrogen peroxide make their use distinctly less desirable. Escharotics such as tannic acid solution, tannic acid-silver nitrate solutions or triple dye solutions should be used only with the realization that they are damaging to normal muscle tissue. Under certain circumstances the latter substances may prove injurious by absorption into the body.

The present study does not concern itself with the effect on the rate of healing of wounds, but it is probable that necrosis would delay it.

SUMMARY

Various substances which have been applied to human burns and wounds were utilized on rats as test animals and their local and general effects noted. No necrotizing effect on the exposed muscle of the rat's abdominal wall was seen when nothing or when isotonic solution of sodium chloride, petrolatum, boric acid ointment or motor oil (Esso no 3) was applied.

White soap, ether and benzene had a minimal but definite necrotizing effect, involving the superficial muscle fiber layer, while hexylresorcinol, solution of hydrogen peroxide U S P (50 per cent dilution), medicinal soft soap U S P (50 per cent aqueous), and alcohol (95 per cent) produced a more pronounced necrosis involving the superficial 2 to 3.5 layers of muscle fibers. Tannic acid 10 per cent, silver nitrate 10 per cent mixtures of tannic acid and silver nitrate and "triple dye" were extremely damaging to rat muscle, to a depth of six to nine layers of muscle fibers.

Absorption of certain of these substances by the large ventral areas denuded of skin was sufficient to cause death, specifically, alcohol (95 per cent), causing acute alcoholism, and solution of hydrogen peroxide U S P (half strength), causing gaseous cardiac embolism. The absorption of benzene caused muscle tremors. Lethal anesthesia resulted if the rats breathed any great quantity of the benzene. Absorbed tannic acid produced hepatic necrosis.

These results indicate possible untoward effects of various substances which have been employed as therapeutic agents or as detergents on human burns or wounds.

On the basis of these tests on rats detergents should be avoided, but if they must be used white soap and ether are the least objectionable of those tested. White soap has the advantage, in comparison with ether, that it is not inflammable.

Mrs Margery Prindle, M A, assisted in this study.

NAVAL CASUALTIES IN A BASE HOSPITAL IN THE SOUTH PACIFIC

LIEUTENANT GEORGE CRILE (MC), USNR

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The treatment of choice of wounds depends largely on the speed with which facilities adequate for definitive treatment can be made available. Surgeons may report excellent results in the treatment of civilian casualties in metropolitan hospitals using methods that would not be applicable to field conditions. When the wounded can be taken immediately to a well equipped hospital or to an undamaged sick bay aboard a capital ship, radical excision of wounds and other operations may be feasible and successful. But in jungle fighting, hours or days may elapse before the wounded reach a field hospital, which usually not only is crowded but is often subjected to air raids or even to artillery fire. Similarly, if the ship aboard which casualties occur is subsequently sunk, the wounded may float for hours before being rescued by a destroyer, whose sick bay may already be filled to overflowing and whose one medical officer has more than he can do. Since a majority of the injuries that I saw were sustained aboard ships that were sunk or during action on land where prompt access to a well equipped hospital was not available, any conclusions drawn from the course of these patients must be interpreted not as being in conflict with reports from other areas but as being applicable to the type of casualties which occurred early in the Solomon Islands campaign.

EVALUATION OF EARLY TREATMENT

The patients received from the combat zone did not arrive at the Naval Hospital in Auckland, New Zealand, until twelve days or more had elapsed since they were injured. During the first few weeks of the campaign, before hospitals were in operation on islands nearer to the front, patients were received directly from hospital ships without previous hospitalization. During this period my colleagues and I saw a true cross section of casualties from the Solomon Islands, an opportunity denied us when hospitals in the north began quite rightly, to

hold over the most seriously wounded for supportive treatment before transferring them to us. Although we had no opportunity for treating freshly wounded patients, we perhaps were better able to evaluate the results of the initial treatment than were those who gave it and subsequently lost track of their patients through evacuation.

From eight to thirty-six hours usually elapsed before the patients reached a place where facilities for definitive treatment were available. At this stage infection was the greatest problem. Most compound fractures and many of the more severe flesh wounds of the extremities had been immobilized in plaster. A majority of these wounds did well when no attempt had been made to close them. However, wounds that had been treated by excision or radical debridement together with primary closure were nearly always badly infected, and it was necessary to open and drain those wounds which had not already broken open. These infections were among the most severe that we saw.

Wounds that had been widely debrided or excised without closure usually did not become infected, but the incidence of infection did not appear to be any lower in this radically treated group than in those in which little or no debridement had been carried out. Incisions made by excision of the wounds tended to gape widely and left large defects which subsequently had to be covered with a skin graft. Since little or no advantage was gained by these operations, and since the incisions increased the deformity and prolonged convalescence, conservative debridement or no debridement coupled with the liberal use of sulfonamide compounds seemed to be the treatment of choice. In most cases this technic was used, and the incidence of gas gangrene appeared to be no higher than when more radical procedures were used. In fact, no gas gangrene was seen in the first 500 or 600 patients treated.

Wounds in which metallic foreign bodies were present healed promptly and with little tendency to infection although if the foreign bodies were over 2 cm. in diameter or located near the surface, a clean draining sinus was apt to persist. Here it was simple to remove the foreign body.

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through the sinus tract without use of anesthesia following which the sinus closed spontaneously. Foreign bodies up to 2 cm in diameter embedded in muscle produced no symptoms, unless they impinged on nerves or were in the proximity of joints. Therefore the immediate removal of deeply embedded foreign bodies was not essential, particularly if the procedure threatened to introduce infection into the depths of a relatively clean wound. Nonmetallic foreign bodies, usually bits of clothing, were either discharged spontaneously or were removed through the sinus along with the metal that carried them in.

The painful dressing of the stumps after amputation often presented a difficult problem. Most of the amputations were of the guillotine variety, and too often the skin flaps had retracted so far that it was not possible to pull them down over the raw stump. This situation could be attributed partially to the impossibility of maintaining adequate skin traction during the patient's transfer and partially to the sacrifice of too much skin at the time of operation. The desirability of saving long skin flaps in the case of patients who were to be transported without application of traction was at first not sufficiently appreciated.

Burns that had been treated by tannic acid or other eschar-producing substances were usually infected. Both healing and skin grafting were delayed as compared with those treated by sulfonamide ointments and pressure dressings. The results obtained by the open treatment of burns were far superior to those that followed the use of eschar-forming substances. It was also shown statistically that the incidence of infection was lower in burns treated by the local application of sulfonamide compounds than in those treated with these drugs given only by mouth.

TREATMENT OF INFECTION

Although the incidence of gross infection in flesh wounds and compound fractures was only 12 per cent and 14 per cent respectively, the treatment of infected wounds constituted our greatest problem. These wounds were treated initially by the local application of sulfonamide compounds, and the majority of the patients also received sulfathiazole by mouth. Consequently, when the patients reached Auckland infections that would respond to sulfonamide therapy were under control, and only those resistant to such therapy remained.

These cases could be roughly divided into two categories: first, those in which the infecting organism was resistant to sulfonamide therapy,

and second, those in which mechanical factors in the wound prevented drainage and allowed pus to accumulate and neutralize the effects of the sulfonamide preparations. In the latter group the establishment of adequate drainage either by irrigation with a catheter or by conservative surgical revision coupled with continuation of sulfonamide therapy, usually resulted in the prompt subsidence of the infection. The following principles were applied to the treatment of infected wounds.

Immobilization—If fever or pain suggested infection in a wound immobilized in plaster, the cast was bivalved, the wound was examined to make certain that no abscess or pockets were forming, and the same cast was then reapplied. If the wound was not immobilized in plaster, a splint was applied. If the temperature was elevated or if there were local indications of cellulitis, the wound was examined every three or four days, care being taken to prevent motion of the part. Provided that no abscess or pocket was present, patients did better with immobilization and infrequent dressings than with intensive treatment.

If mechanical factors blocking drainage were present, a conservative surgical revision was performed.

Wet Dressings—Efficient drainage was provided by wet dressings. By catheters incorporated in the dressings, the wound could be irrigated without moving the extremity or changing the dressings. Secretions from the wound soon coagulated on dry dressings and blocked further drainage. Similarly packing the wound open with gauze did not provide satisfactory drainage, unless the gauze was kept saturated to prevent coagulation of secretions.

No Dressings—Certain wounds around the buttocks and rectum were difficult to dress and were subject to contamination by feces. To avoid the discomfort and activity involved in the frequent changing of dressings, patients with wounds of this type were allowed to lie on wax paper, which could be changed as often as necessary with a minimum of discomfort. When fecal fistulas draining posteriorly were present, the patients were placed on Bradford frames and bedpans were placed beneath the frames to catch the discharge. The wounds healed as cleanly without dressings as those which one attempted to keep covered with clean dressings.

Painful wounds, especially of the hands, and raw amputation stumps, to which gauze invariably adhered and caused much pain, were often covered with sterilized cellophane from packages of cigarettes.

Sulfonamide Compounds—A majority of the infections were resistant to sulfonamide preparations, either because of local conditions or because of the type of infecting organism. Therefore these drugs were given by mouth only when the patient showed an elevation of temperature or other evidence of a spreading infection. We used both sulfanilamide and sulfathiazole locally and could see no difference in the efficacy of the two compounds.

The fact that certain infections did not respond dramatically to sulfonamide therapy should in no way reflect on the efficacy of the drugs. Patients were treated with sulfonamide compounds for ten days or more before they reached our hospital, and the value of these drugs was expressed more in the low incidence of infection than in their effect on infections which had already developed.

There is no danger of overabsorption of the sulfonamide preparations from a granulating surface. Only when the drugs are used in extensive fresh burns or are implanted in the peritoneal cavity does this danger exist.

Patients are rarely sensitized to sulfonamide compounds given by mouth. But when they are applied to a raw surface over a long period many patients become sensitized. If a patient has been sensitized by the topical application of one of the sulfonamide drugs, its administration by mouth or to a wound causes a rash to appear promptly at the site of the original application. The rash usually spreads rapidly to involve the entire body and may be accompanied by fever. When the reaction is localized, the rash and fever may simulate lymphangitis and prompt the physician to give increasing amounts of the drug until the true nature of the complication is recognized.

Operation—Few infected wounds required surgical treatment. Deep abscesses were rare, and the only foreign bodies which caused significant reaction in the tissues were the nonmetallic ones or occasionally pieces of aluminum. Frank suppuration was usually present about nonmetallic foreign bodies and it was a simple matter, usually without anesthesia, to grasp them with a hemostat and withdraw them through the sinus tract. Similarly, bits of shrapnel that caused persistently draining sinuses could usually be felt with a probe and withdrawn with a hemostat without undue discomfort to the patient.

Large subcutaneous or intramuscular pockets were treated satisfactorily by (1) immobilizing the part, (2) inserting a catheter into the pocket, (3) irrigating the wound through a catheter every two hours day and night with sulfanilamide suspended in a 1:500 solution of chloroazodin

(azochloramide) and (4) applying a pressure dressing after forty-eight hours of irrigation. Often when the catheter was removed after four or five days only the sinus tract remained.

A wound which does not respond within a week to intensive treatment with sulfanilamide suspended in chloroazodin solution will probably never respond to that form of therapy. In these cases surgical measures were no longer deferred, and the pocket was opened and packed open. Skin was never sacrificed unless the infection was of a burrowing necrotizing type. When the skin was conserved most wounds could be closed without utilization of grafts. Although defects left by this procedure often required secondary closure, this was preferable to a prolonged period of drainage from a chronic abscess.

SECONDARY CLOSURE

The rate of healing of wounds varies greatly in different patients. This variation appeared to be related to factors other than the presence of gross infection or to a deficiency of vitamin C. The factors which influence the rapidity with which a clean wound closes of its own accord have not been determined.

Wounds close by contraction and by epithelization, these processes go on at various rates in different persons and in different locations on the same person. Wounds of the leg, particularly over the tibia, and wounds about the hip are usually slow in closing. An underlying bone, such as the tibia, seems to interfere with contraction of the wound and the blood supply necessary for growth of epithelium. The difficulty of immobilizing the hip without using a body cast may be responsible for failure of wounds of the hip to heal.

The size of a wound does not necessarily determine the advisability of closing it. In general, wounds over 2 inches (5 cm) in diameter should be closed, but occasionally a wound of this size will contract and epithelize so fast that spontaneous healing will occur nearly as rapidly as solid union after closure. On the other hand, many wounds only one-half inch (1 cm) in diameter may reach a stage of complete equilibrium in which no further contracture or epithelization takes place. This situation usually occurs in wounds over the tibia, but may occur in any wound of long duration when the blood supply and ability to contract are limited by base of dense scar tissue.

Since at first glance it is impossible to determine whether a wound will heal spontaneously or whether operative treatment is indicated, a wound should be observed.

closure is advised. During this time any residual infection can be cleared up so that the operation may be performed in as clean a field as possible. Many fresh wounds which at first seemed to require closure will have healed so fast during this period of preparation that operation will not be necessary.

On the other hand, if a small wound, even $\frac{1}{2}$ inch or less in diameter, reaches a stage when its edges appear totally inactive and when it has remained the same size for a week or longer, time will be saved if a secondary closure is done immediately. The time for closure may be determined only by observing the wound and noting its failure to make progress under adequate conservative treatment.

In general, wounds do not show a maximum healing tendency until two weeks after they have been sustained. By this time the infection usually has subsided, and the wound is granulating cleanly and beginning to contract and epithelize. If a wound is two or more months old, it will rarely exhibit a dramatic healing tendency and will often develop the chronicity of an ulcer. Therefore it is a good rule to act promptly in closing old wounds, and to delay in closing small wounds of recent origin. Fresh wounds of large size heal according to the law of diminishing return, the wound may heal rapidly at first and then, as scar tissue forms at the base and impedes circulation and contraction, the wound may heal more slowly, or may never heal. It is unwise to expect the rapid spontaneous closure of a large wound, no matter how fast at first it may appear to be closing.

Secondary Closure vs Skin Grafts or Spontaneous Epithelization—Whenever possible, closure of a defect by suture is preferable to the grafting of skin. After closure, the surface is composed of normal skin and subcutaneous tissue and is much more resistant to trauma than is even a thick skin graft. Closure reduces scarring, and if the deeper tissues are not injured the patient is fit to return to duty as soon as the wound is solidly healed. A skin graft must be protected from trauma for weeks or even months and may never afford an entirely satisfactory surface in locations subjected to weight bearing or trauma.

Extensive scarring, resulting from spontaneous epithelization, is similarly undesirable. The epithelium is thin and lacks the supportive structures of normal skin. The slightest trauma may cause this type of epithelium to break down repeatedly, or if the scar is at a joint, its contraction may limit motion. Secondary closure therefore is the treatment of choice for all large

wounds which will heal with a broad scar that might be the site of future trouble.

It is difficult to decide when to graft skin and when to close a wound by suture. In most wounds the defect in the skin is more apparent than real. The same elasticity of the skin which results in wide separation of the wound edges, particularly after radical debridement, often allows it to be closed again by suture. However, when skin has been avulsed by shell fragments in wounds of exit, or when primary closures have broken down with loss of the skin edges, the defect may be too large to close without grafting. Here grafting should be deferred until the wound is clean, and until all sinuses have filled. After suitable preparation of the surface, a split-thickness skin graft should be applied.

The success of a secondary closure depends primarily on the ability of the surgeon to immobilize the part and to apply an efficient pressure dressing. If a snug pressure dressing can be applied by a circular elastic bandage wounds of the arms or legs can be closed even under considerable tension. Wounds about the hip, however, are subject to motion with every movement of the trunk or legs, unless a spica cast is used, and pressure is difficult to apply. If there is much tension in an area subjected to motion, the sutures tend to cut through and the wound edges to separate, resulting in a failure of the closure. Consequently, although wounds of the legs or arms under extreme tension may be closed by sutures, wounds of the hip should be covered with skin grafts unless the skin edges can be brought together with ease.

Wounds of the muscular portions of the legs or arms can be undercut widely so that the edges can be approximated, and firm pressure dressings applied without jeopardizing the circulation of the skin flaps. Wounds over the tibia must be treated more carefully, for if the skin flaps are widely undermined the pressure of the dressing against the tibia may cut off the circulation and cause necrosis of the skin edges.

Similarly, when a flap is to be swung from the side of the leg over the tibia, it should first be elevated and replaced in its bed for two weeks before final transfer is effected. The circulation of the skin of the leg is not so good as elsewhere, and when flaps are longer than the width of their bases, it is safer to transfer them in stages.

Technic of Secondary Closure—If a defect is to be covered with a skin graft, the surface should be as clean and the granulations as healthy as possible. If the wound is to be closed, however, it is not so important for the granulations to

be flat and red as if a graft were to be applied. Although a closure usually can be accomplished successfully in the presence of considerable discharge, there should be no unclosed sinus tract leading to a pocket from which infection can spread and involve the entire wound. Preparation for secondary closure of a clean granulating wound usually consists of sprinkling sulfanilamide powder on the wound twice daily for two days and applying a pressure dressing saturated with chloroazodin solution.

The operation is performed with the patient either under local anesthesia or under anesthesia with pentothal sodium and consists of the following steps:

- 1 Granulation and scar tissue is excised down to normal muscle or fat. When nerves, vessels, tendons or other important structures are in the vicinity only the granulations are shaved away. Although the results seemingly are not so good as when scar tissue is completely excised, the number of failures does not warrant the risk of damaging important structures.

- 2 The skin is undercut sufficiently to accomplish satisfactory closure.

- 3 Hemostasis is obtained chiefly by pressure dressings; no attention is paid to venous or capillary oozing. Spurring arteries are ligated with no. 50 or 60 cotton. No catgut is used because it tends to cause reaction in the tissues and result in the development of infection. Few or no ligatures are used, and in our experience there has been no difficulty with cotton being discharged from these wounds.

- 4 The entire wound is dusted with sulfanilamide powder.

- 5 The skin edges are approximated with vertical mattress sutures of no. 32 stainless steel wire by taking large bites. No rubber gauze or other material is placed between the loops of the sutures and the skin to prevent the wires from cutting through. Wire with the aid of a pressure dressing holds the skin together long enough to insure adherence of the edges; if the wire does cut through, only small vertical slits are left instead of large areas of necrosis resulting from pressure of the material designed to keep the wire from cutting. Moreover, the circulation of the skin edges is not jeopardized by the pressure of broad pieces of rubber under the wire loops. Therefore in wounds closed under extreme tension it seems preferable to accept the cutting of a small loop of suture rather than to jeopardize the circulation of the entire edge of the wound with pressure from various devices designed to prevent the sutures from cutting.

- 6 If considerable oozing is present or if the wound is grossly contaminated, a small rubber drain is inserted through the skin edges at the dependent part of the wound.

- 7 A gauze dressing is applied to the wound, and over this sterile mechanic's waste (cotton) is placed to assure an even distribution of pressure. Pressure is then applied with a woven elastic bandage.

- 8 If the wound involves a joint, the joint is splinted to insure absolute immobility.

- 9 The wound is inspected for the presence of infection after five days; if it is healing well, the pressure dressings and splints are reapplied. The sutures are

not removed for two or three weeks, even if they tend partially to cut through the tissues.

The incidence of infection in these cases is low and the results when pressure and immobilization can be maintained are good even when the wounds are closed under great tension.

FOREIGN BODIES

Indications for Removal—Many metallic foreign bodies cause no symptoms. If they are not (1) over 2 cm in diameter, (2) located in the region of a joint, (3) impinging on a nerve, (4) located subcutaneously or (5) causing a draining sinus, they may remain embedded in the tissues indefinitely without causing trouble. This is particularly true if the patient is not aware of their presence. The deeper a foreign body is embedded the less apt it is to cause symptoms. Foreign bodies over 2 cm in diameter, even when deeply embedded in muscle or fibrous tissue, occasionally cause symptoms requiring their removal.

Foreign bodies located directly under the skin are often palpable, and since they are readily removed, it is wise to do so. Superficially located foreign bodies are more apt to cause persistently draining sinuses. Occasionally their proximity to a joint necessitates their removal.

When a patient complains of pain in an extremity and a roentgenogram shows a foreign body embedded in the tissues, a logical assumption is that the pain is caused by the foreign body. However, this is rarely the case. The pain is usually the result of a traumatic neuritis and is not related to the metallic fragment. When a nerve has been damaged or cut, a traumatic neuritis ensues and for weeks or months pain may be referred to the distribution of that nerve. Most patients who complain of pain in an extremity and who show no evidence of infection have sensory changes in the skin corresponding to the distribution of one of the sensory nerves. Hyperesthesia, hypesthesia or anesthesia may be present, and careful roentgen studies usually will show that the foreign body is not located anywhere near the course of the nerve supplying the area to which the pain is referred. Under these circumstances, removal of the foreign body is not indicated; time will heal the symptoms of injury to the nerve. The less the patient knows about the presence of the foreign body, the more apt the symptoms are to subside promptly.

Technic for Removal of Foreign Bodies—Both anteroposterior and lateral roentgenograms should be used to locate foreign bodies accurately before their removal is undertaken. If a report

on a roentgen examination states that a foreign body 2 cm in diameter is present in a certain location in which a mass is palpable, one might assume that the palpable mass is the foreign body. Too often a tiny foreign body, the size of a grain of wheat, is surrounded with a hematoma which causes the palpable mass, while the large foreign body which is to be removed is located elsewhere. A small foreign body traveling at high velocity may penetrate a bone without fracturing it and may leave a palpable area of reaction along its course, so that the impression is given that the foreign body is palpable over the bone. For this reason, skin markers or fluoroscopy should be used, and anteroposterior localization should be carried out. The two needle system of localizing a foreign body may also be of value.

Through the courtesy of an Army General Hospital we had access to a Burman Locator, an instrument which indicated the location of a metallic foreign body. The instrument is so large, however (its point is nearly the size of a thumb), that it is not of much value in locating the small foreign bodies that are the most difficult to find. The instrument is of unquestionable value in locating larger foreign bodies deeply embedded in the tissues and has proved to be a useful adjunct to roentgenography and fluoroscopy. In locating smaller fragments, the fluoroscope is of the greatest value.

BURNS

Initial Treatment—During the first year over 200 patients with burns were treated at our hospital. Only a few of these burns were fresh, the majority being from ten days to three weeks old. In the beginning nearly all burns had been treated with tannic acid. Later the majority had been treated with sulfonamide ointments and pressure dressings. The results of treatment with sulfonamide ointment were incomparably superior to those obtained with eschar-forming substances. The incidence of infection was lower, and grafting of skin could be done much earlier. It made little difference which sulfonamide compound was applied if the burn was considered to be a contaminated open wound and no eschar-producing substance was used. Our preference for the initial treatment of burns was sulfathiazole ointment and pressure dressings, the initial dressings being left on for a week or more unless evidence of sepsis developed.

Treatment of Infected Burns—Infection was the greatest problem in the majority of burns at the stage in which we saw them. Nearly all third degree burns and about 20 per cent of

second degree burns treated with tannic acid were grossly infected.

Dressings and soaks with 1:500 aqueous solution of chlorazodin and saline solution were most effective in softening eschars and controlling infection. As soon as the eschars could be removed intensive treatment was commenced to control infection and to prepare the surfaces for skin grafts.

Preparation of the Wound for Grafting—[I quote from an earlier article.] The use of the sulfonamides alone does not always clean up the infection and prepare the granulating surface for grafting. Often the granulations remain boggy and edematous and continue to be covered with purulent exudate in spite of the daily application of either sulfanilamide or sulfathiazole powder. The combined use of moist saline dressings and sulfanilamide resulted in striking improvement of many of these wounds, but the best results were obtained when the wounds were

- 1 Sprinkled with sulfanilamide
- 2 Dressed with fine-mesh gauze saturated with a 1:500 solution of azochloramide in glyceryl triacetate
- 3 Covered with gauze dressings saturated with saline
- 4 Bandaged with an elastic bandage to give pressure
- 5 Kept moist with saline injected into the dressing through catheters

Moreover whenever the burn was on an extremity, this was elevated to afford dependent lymphatic drainage. Forty-eight hours after this type of dressing was applied usually there was produced a clean, firm, red granulating surface on which skin could be grafted without necessitating cutting off the granulations. The dressings were usually changed only twice during this forty-eight hour period.

Sulfanilamide, when not inhibited by the presence of pus and products of proteolysis, will quickly clean up most infections that may be present on a granulating surface, but if pockets, recesses, or sinuses in which pus can form are present sulfanilamide will be inactivated and the infection will persist.

The combined use of sulfanilamide and azochloramide [chlorazodin] appeared to be much more effective than the use of either drug alone.

The pressure dressings not only reduce the amount of exudate and thus decrease the inhibitory effect that this exudate will have on the sulfanilamide, but also reduce the edema of the granulations and make them firm, vascular, and ready for grafting.

The moist dressings prevent caking of the sulfanilamide powder and allow free drainage of the exudate. If dry dressings are applied they soon trap further secretions beneath an impervious layer of caked exudate and thus inhibit the activity of the sulfanilamide.

If the extremity is elevated, gravity aids in reducing the edema of the granulations, and the exudate appears to diminish in amount. It is thus clear that each step in this plan of treatment plays a part in diminishing or removing the exudate or in neutralizing its inhibitory effects on the activity of the sulfonamides.

1 Crile, G., Jr. Experiences of Surgical Service of United States Naval Hospital, Auckland, New Zealand, with Casualties from Initial Solomon Islands Engagement, U. S. Nav. M. Bull. 41:306 (March) 1943.

The oral administration of the sulfonamides did not seem to be of any particular value in the treatment of infections in which pus had formed beneath eschars.

In many cases, changing dressings is a painful procedure, especially when the burns involve the hands. Even moist fine mesh gauze tends to adhere to the raw surfaces and not only causes pain but also destroys the young epithelium. Although with perfectly clean lesions petrolatum gauze or ointments of various types do not have the liabilities of gauze, neither petrolatum nor any ointment allows free drainage of the secretions. When drainage is blocked, pus accumulates, granulations become boggy and edematous, the efficacy of a sulfonamide compound is reduced by the presence of peptones, infection does not clear up, and the area cannot be rendered clean enough to apply a graft. Petrolatum or any oily substance converts an infected surface into an abscess, one wall of which is the granulating surface and the other the gauze impregnated with petrolatum. A dressing is needed which will afford drainage and at the same time will not adhere sufficiently to cause pain or to damage young epithelium when it is removed. Such a dressing was suggested by Callahan,² who used an absorbent cellulose compound, "Kleenex." Kleenex can be autoclaved and applied directly to open wounds or raw surfaces. It is extremely absorbent, allows free drainage of secretions if dressings are kept moist and is practically nonadherent. If it does tend to adhere, moistening causes almost complete dissolution of its fibers. Pain and damage to tender epithelial strands can be prevented if this type of dressing is used on burns.

For badly infected lesions irrigations with a saturated solution of sulfanilamide are alternated with chlorazodin solution. Once or twice a day a solution of 1 per cent acetic acid is introduced to control any infection with *Bacillus pyocyaneus*. But the most important feature of the preparation of the area for grafting of skin is the application day and night of wet pressure dressings which are never allowed to dry.³

PENETRATING WOUNDS OF THE CHEST

Most penetrating wounds of the chest produced a hemothorax or hemopneumothorax. These complications were usually mild and soon cleared up spontaneously, especially when the

wound was inflicted by the small caliber Japanese bullets. The incidence of empyema in these cases was low.

Empyema almost always developed in large sucking wounds of the thoracic wall produced by shell fragments. The foreign bodies rarely lodged in the pleural cavity or lungs but usually either penetrated both walls of the thorax or after traversing the pleural cavity came to rest in the opposite thoracic wall.

Hemothorax was treated conservatively. The patients were confined to their beds, and sulfathiazole was given by mouth. The blood was not aspirated unless (1) the patient became dyspneic, or (2) persistent, steadily rising temperature and evidence of sepsis indicated the development of infection.

The incidence of empyema was low (probably not over 10 per cent). There were no fatalities from empyema although the entire pleural cavity was usually involved. The average patient with a large hemothorax may have a temperature as high as 103 F for two or three weeks, suggesting the presence of empyema. At the end of this time, the temperature may begin to subside spontaneously and return to normal levels in four or five weeks. Therefore either open or closed drainage of a hemothorax should be postponed until repeated cultures of fluid aspirated from the chest have indisputably proved the presence of infection.

In empyemas resulting from wounds the fluid does not contain as much fibrin as in postpneumonic empyemas, nor does the pleura or fluid thicken as rapidly. Therefore the fluid may be aspirated for a considerable length of time after infection develops. We did this in several instances and did not observe infection of the wall of the chest. It was my impression that by emptying the infected pleural cavity each day without introducing air it might have been possible to have decreased the size of the cavity which resulted when open drainage was finally established. When this can be accomplished convalescence will be shortened unquestionably.

PENETRATING WOUNDS OF THE ABDOMEN

As a result of conditions of combat few patients with abdominal wounds were seen at the base hospitals. Operations to repair injuries of the bowel usually were done a number of hours after injury and it was surprising that any of the patients survived. In most instances incisions had been closed with catgut, and almost without exception these wounds had become infected and usually had disrupted. I believe that better results would have been obtained if the wounds

2 Callahan, G. B. Burns Treated by Cod Liver Oil Treatment—Paper Tissue Dressing, *Mil Surgeon* 92:439 (April) 1943.

3 Full details of the routine used by the Burn Service under the direction of Lieutenant H. R. Yandell are pending publication in the *U. S. Naval Medical Bulletin* for April 1944.

had been closed with nonabsorbable suture material or had been packed open

Most of the fistulas of the small intestine closed spontaneously. The same was true of a biliary fistula, presumably arising from the gallbladder. Frequently, injured segments of the colon had wisely been exteriorized, or a proximal colostomy had been performed. In these cases it was a simple matter to close and replace the colon.

INJURIES TO ARTERIES

Secondary Hemorrhage—Bleeding may occur into a cast with no external evidence of hemorrhage except shock. As the patient himself is often unaware of the bleeding, this complication must always be suspected when a patient with a cast suddenly exhibits symptoms of shock.

Ligation of a vessel as large as the femoral artery when conducted in an infected field is usually doomed to failure. After three or four days the ligature is thrown off the artery and the bleeding recurs. Whenever possible the vessel should be ligated through a separate incision in a clean field. As a rule packing does not control hemorrhage from a large vessel for more than a few hours.

On several occasions we were surprised to find that bleeding from the infected wound persisted or recurred after proximal ligation of the main vessel through a separate clean incision. In these cases the distal end of the main vessel was bleeding by means of collateral anastomosis. Because the pressure in the distal end of the vessel is so low, simple ligation of the distal stump in the infected field permanently controls the bleeding.

Communicating Arterial Hematoma (Pulsating Hematoma)—When the wall of a vessel is not completely severed by a small projectile but has an opening in one side which is held open by elasticity of the vessel, blood escapes into the tissues. Clots block the wound of entry, and a pulsating hematoma is formed. The wound of entry soon heals over, and a hematoma remains which communicates with the artery. Clinically, this manifests itself by a tense, fluctuating mass which has an expansile pulsation if located superficially and over which a systolic bruit frequently can be heard. It is differentiated from an arteriovenous aneurysm by a bruit which is audible only in the systolic phase and by the absence of circulatory signs attending an arteriovenous fistula. Occasionally, when the hematoma is located deep under the muscles and fascia and when the opening in the vessel is small, there is no bruit or palpable pulsation; the diagnosis is established by inserting a needle and obtaining bright red arterial blood.

The hematoma is under full arterial pressure and gradually enlarges until it ruptures spontaneously through the skin, usually at the site of the wound of entry. The defect must be repaired before a severe secondary hemorrhage occurs. The treatment of choice is ligation of the vessel above and below the point of injury, division of the artery and ligation of its accompanying vein. Since it is often impossible to apply a tourniquet proximal to the lesion, it may be necessary to control bleeding by placing a tape around the vessel through a separate incision. In this event it is desirable also to place a tourniquet distal to the wound in order to control bleeding from the distal end of the vessel.

The sacs of the false aneurysms are not excised, but are merely sprinkled with sulfanilamide powder and then obliterated by very light pressure. The wounds heal promptly without infection or secondary hemorrhage.

Reconstruction of a vessel is rarely desirable since thrombosis or development of a true aneurysm frequently occurs. We had occasion to ligate the common carotid artery, the femoral, the subclavian and the axillary, and on two occasions both the femoral and profunda arteries without observing serious impairment of the circulation.

Circulatory Disturbances Following Injury of Blood Vessels—Damage to the great vessels, even in young people, may cause gangrene of the extremity, but in our experience this complication occurs only (1) when the wound is large and when much muscle and many collateral vessels are destroyed, (2) when severe infection and swelling interfere with collateral circulation or (3) when the injured artery is the popliteal. Since most communicating arterial hematomas are caused by small projectiles and since few are infected, maintenance of adequate circulation is not often a serious problem.

Impending circulatory gangrene of an extremity, resulting from extensive destruction of soft tissues and blood vessels, can be satisfactorily treated for several weeks by conservative means, if facilities are available for refrigerating the gangrenous extremity. During this time collateral circulation develops (aided, if desired, by injection of procaine hydrochloride into the sympathetic nerves and by the oral administration of alcohol), and the line of demarcation which then develops is often considerably lower than was initially expected. By keeping the gangrenous portion cool, infection can be retarded or prevented until collateral circulation

of the viable portion permits good healing after amputation. The gangrenous portion must be examined frequently for signs of infection.

Arteriovenous Fistula—Repair of an arteriovenous fistula is not an emergency procedure. Unlike communicating arterial hematomas in which the sac expands under tension of full arterial pressure, the blood in an arteriovenous fistula is under low pressure and hence the aneurysm does not tend to rupture externally. The pressure is shunted off into the veins, and the only dangers are chronic circulatory disturbances in the extremity and overburdening of the myocardium.

Since blood pressure in the extremity is low as a result of deflection of arterial blood into venous channels, collateral circulation soon develops. Although most aneurysms could be corrected immediately by quadruple ligation of the vessels, it is wise to wait two or three months until collateral circulation has developed beyond the point of slightest question.

GAS GANGRENE AND TETANUS

Tetanus, to my knowledge, did not occur in the South Pacific area. The absence of tetanus can be explained by the fact that all men engaged were actively immunized with tetanus toxoid, and booster doses of toxoid were always given as soon as a wound was incurred.

Gas gangrene was not common. During the first six months we encountered no cases of gas gangrene, and in all only 15 or 20 patients proved to have such a condition were admitted to the hospital. Since some amputations were performed for suspected gas gangrene in forward areas a statistical analysis of its incidence was impossible.

It was interesting that the incidence of gas gangrene was so low, because little gas gangrene antitoxin was used prophylactically in the first six months, and few of the wounds were radically debrided. From this it should not be inferred that debridement and prophylactic doses of gas gangrene antitoxin are not of value. Reports from other areas often indicate that the opposite is true. It is likely that the clean environment of ships and the lack of cultivation of the soil had as much to do with the low incidence of gas gangrene as did any therapeutic measures. But in connection with the prophylactic value of excision of wounds or radical debridement it is interesting to note that Major McLennan of the British Army, reports the incubation period of infections due to *Clostridium welchii*—from time of injury until development of clinical symptoms of infection—to vary from seven hours to three and one-half days with an

average of twenty-three hours.⁴ Accordingly, one would scarcely expect wound excision, performed twenty-four hours or more after the wound is sustained, to effect any striking diminution in the incidence of gas bacillus infection.

Gas bacillus infection may vary in severity from (1) a very mild type, slow to develop, slow to spread, and easily controlled by removing the involved muscle bundles and affording adequate drainage, to (2) a fulminating variety, initiated by profound systemic symptoms and progressing, despite treatment, to prompt and certain death. Approximately one fourth of our cases were in the latter category.

In fulminating gas gangrene systemic signs may overshadow the local manifestations of the infection. Often the gas is not palpable in the tissues, and the odor is not detectable. Instead manifestations of shock first call attention to the seriousness of the patient's condition.

Shock develops because of diminution in blood volume. In fulminating gas gangrene infection enormous amounts of fluid are lost into the tissues in the production of edema, and large quantities of serosanguineous fluid pour from the wound. When a wound begins to bulge and pour out serum, gas gangrene must always be suspected, as these are usually the initial signs. The presence of crepitus or of gas coming from the wound may be found only in the terminal stages.

As soon as gas gangrene is suspected, smears should be made. If characteristic bacilli are found, large quantities of polyvalent antiserum should be given without delay. After a corneal test for hypersensitivity, the serum should be given intramuscularly—some of it around the wound—in doses up to 100,000 units within four or five hours. In our experience the intravenous administration of the serum produced severe reactions and was discontinued.

Gas bacilli grow in dead tissue and produce a toxin that kills adjacent living tissue; they then spread to recently killed tissue, again forming toxin, and progressively involve more and more of the body. Since sulfonamide compounds have only a slightly inhibiting influence on the organisms, and since the drugs are blood borne and hence do not reach the areas of dead tissue in which the organisms are growing, not much reliance can be placed on their use. Roentgen therapy in our experience is of little or no value. The only hope is (1) to remove or drain the focus of infection and (2) to raise the antitoxin

⁴ McLennan, J. D. Anaerobic Infections of War Wounds in Middle East. *Lancet* (a) 2: 63 (July 17) (b) 94 (July 24) (c) 123 (July 31) 1945.

levels high enough to neutralize the toxins and prevent them from killing more tissue

Organisms other than the gas bacillus can produce necrotizing infections of the muscle. Major MacLennan reported 8 cases of an anaerobic streptococcal infection of the muscle, which resulted in gangrene of the involved tissues.¹⁴ In a case that we observed several entire muscles of the forearm became gangrenous and were discharged from the wound. Cultures failed to grow the gas bacillus, and smears showed a predominance of streptococci. In such cases and also in cases in which air is blown into the tissues, gas bacillus infection may be erroneously suspected and amputation unwisely performed.

TROPICAL DISEASES

Tropical Ulcers—The causation of tropical ulcers is not known. Following insignificant trauma, such as scratching a shin, bruising an ankle or an insect bite, a small ulcer develops. These ulcers become chronic and continue to enlarge in spite of seemingly adequate therapy. Even when treated intensively with bed rest, sulfonamide compounds and pressure dressings they often will stubbornly refuse to heal until the patient is evacuated from the tropics. Cultures taken after several weeks fail to reveal any specific organisms in the ulcer.

The majority of the ulcers were on the lower leg, usually over the tibia. Most of them had been present for two or three months, their bases were filled with edematous granulations and the epithelium was completely indolent, showing no tendency to grow over the surface of the ulcer.

The ulcers varied from 1 to 10 cm. in diameter, the majority measuring from 2 to 3 cm. Even in the temperate climate of New Zealand and when the patients were treated with rest in bed, sulfonamide drugs, chloroazodin solution and pressure dressings healing was apt to be remarkably slow. For this reason surgical measures was the treatment of choice in these cases.

The epithelium of an ulcer which heals spontaneously over a period of months is paper thin and is apt to break down under the slightest trauma. This is particularly true when the ulcer is over the tibia, a site having a poor blood supply and vulnerable to trauma. For this reason, and because of the time required for these lesions to heal spontaneously, the ulcer is excised and the defect is either closed or covered with a skin graft. When the ulcer is over the tibia and is too large to excise and close, a flap from the lateral surface of the leg can be swung

over it, and the area from which the flap was taken can be grafted at the same time. A good base is thus afforded for the graft, and a good covering of skin and subcutaneous tissue is swung over the tibia. In lesions of the lateral parts of the leg subcutaneous tissue is usually sufficient to allow excision of the ulcer and immediate application of split-thickness skin grafts.

SUMMARY

No striking benefit is to be expected from radical debridement or excision of the wound when it cannot be done in the first few hours.

Wounds debrided and closed eight hours or more after they are sustained almost invariably become infected and break down.

Long skin flaps should be left when amputations are performed, especially on patients who are to be evacuated and on whom adequate skin traction cannot be maintained.

Infection is treated by the use of sulfonamide compounds and chloroazodin, revision of the wound is performed and the infected part is immobilized.

Early secondary closure is desirable, and the technic outlined may be used for accomplishing this.

The presence of metallic foreign bodies usually does not interfere with healing, when a draining sinus persists, the foreign body is easily removed through the sinus.

The results of treatment of burns with tannic acid are not as good as those obtained from the use of sulfonamide ointments and pressure dressings.

Infected burns should be prepared for grating of skin as discussed, and wet dressings, sulfanilamide powder, chloroazodin and pressure dressings should be used.

Hemothorax usually absorbs spontaneously with no treatment other than with the sulfonamide preparations and bed rest.

Communicating arterial hematomas are treated by prompt ligation and division of the injured artery. Circulatory gangrene rarely follows ligation of the great vessels, unless collateral circulation has been destroyed or severe infection has occurred.

The incidence of gas gangrene is low, but approximately one fourth of the cases are of the fulminating type. Early surgical treatment and the prompt use of large doses of antiserum is the treatment of choice.

Early excision and closure of tropical ulcers is desirable.

COMPARATIVE VALUE OF SOME BLOOD SUBSTITUTES USED FOR TREATMENT OF EXPERIMENTAL SHOCK

CHARLES C SCOTT, M.D., PH.D., AND HAROLD M WORTH, A.B.
INDIANAPOLIS

AND

LIEUTENANT E BROWN ROBBINS, U.S.N.R.

In shock resulting from hemorrhage, trauma or burns, therapy with intravenous injection of fluid is well established as decidedly beneficial. Numerous investigations deal with the value of blood and various blood substitutes in shock. This is partly owing to the desire to find a blood substitute which is highly efficient, readily available, relatively inexpensive and completely safe. Plasma or serum fulfills all requirements except that it is costly. In addition, to bring it to a readily available form, a vast amount of work is required. The great value of plasma outweighs these objections during emergencies such as the present war. In peacetime, these difficulties have considerable practical importance.

Although the use of blood substitutes in the treatment of shock has been widely studied, the results have often been conflicting. In such circumstances, further work is indicated, with attempts to control or standardize procedures more effectively. The present report is concerned with a comparison of results obtained with a number of well known blood substitutes tested in a relatively pure form of traumatic shock.

METHOD

Although our procedure for applying venous tourniquets was published previously,¹ the method may be reviewed briefly. Dogs weighing 12 Kg or more were used. They were kept in air-conditioned quarters for at least one week prior to their use. The procedure and recovery took place under the same environmental conditions. Free access to water was allowed the animals preceding and following the experiment. The dogs were usually starved for at least eighteen hours before the tourniquets were applied. A dose of 25 mg per

kilogram of secenal sodium (sodium 5-allyl-5(1-methyl-butyl) barbiturate) was given intraperitoneally for anesthesia. Thereafter, throughout the period of application of the tourniquets, one-tenth the anesthetic dose was injected intraperitoneally as necessary to maintain light anesthesia. This resulted in no deaths from the anesthetic, which agrees with the observations of Mylon and his associates² for pentobarbital. Mean blood pressure was recorded in the carotid artery by cannula and mercury manometer, clean but not entirely aseptic technic being used. Then a pneumatic venous tourniquet was wrapped snugly around each thigh just below Poupert's ligament. The tourniquets were inflated to equal the mean pressure in the carotid artery. Subsequently, whenever the blood pressure changed the tourniquet pressure was readjusted. Thus, they never became arterial tourniquets. When a shock index³ of 120 was attained, the tourniquets were removed. All untreated animals died. The dogs apparently were all at the same level of shock at the time the tourniquets were removed. Furthermore, this appeared to be relatively early shock. A group of 103 dogs was carried to this level. In an additional series of 21 animals a shock index of 180 was used. This was a more severe degree of shock than the former.

Following release of the tourniquets, infusion of a blood substitute into the femoral veins was started immediately. The volume administered was the amount calculated to cause the blood volume to return to the original value. This was determined with hematocrits just prior to application of the tourniquets and again when they were removed. On a basis of body weight, however, the various groups of animals all received approximately the same volume of fluid. The blood substitute was infused at a moderate speed—thirty to sixty minutes being required to complete the infusion. The carotid artery was then ligated, the cannula removed, and the wound in the neck sutured. If the animal survived for forty-eight hours, it was considered to have recovered from shock. Most of the dogs which lived for two days made complete recoveries, although a few animals died from such secondary causes as infection.

The blood substitutes tested were dog plasma, isotonic saline solution and solutions of gelatin, pectin and polyvinyl alcohol. In the citrate series, fresh plasma from individual dogs was given to one-half

From the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis.

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1 Scott, C. C., and Robbins, E. B. Production of Experimental Shock in Dogs by the Use of Venous Tourniquets, *J. Indiana M. A.* **36** 194 (April) 1943.

2 Mylon, E., Winternitz, M. C., and de Suto Nagy, G. J. Studies on Therapy in Traumatic Shock. *Am. J. Physiol.* **139** 313 (June) 1943.

Duration of tourniquet

$$3 \text{ Shock index} = \frac{\text{Blood pressure fall (\%)} \times \text{application (minutes)}}{\text{Mean blood pressure at time of removal of tourniquets (mm Hg)}}$$

the group, while the remainder received plasma pooled from 10 animals. Heparinized plasma was also unpooled, but freshly prepared. Gelatin U S P was used as a 7 per cent solution in 0.75 per cent sodium chloride and 0.25 per cent sodium bicarbonate. Pure citrus pectin N F in 3 per cent concentration in isotonic saline solution was autoclaved according to the procedure of Bryant, Palmer and Joseph.⁴ Polyvinyl alcohol was dissolved in Ringer-Locke solution, concentrations of both 3 and 6 per cent being tested. This solution was sterilized by passage through a Seitz filter. The polyvinyl alcohol was obtained from Dr. N. W. Roome, of Toronto, Canada, who had used it with success in treatment of hemorrhage in dogs. Except for pectin and polyvinyl alcohol, the solutions were not prepared with sterile technique. It is common experience that dogs withstand intravenous infusions of clean but unsterile solutions without development of septicemia.

RESULTS

A total of 124 dogs was tested, 15 of which received no treatment to serve as controls. These 15 animals died. The effects with the various blood substitutes in early shock are shown in table 1. It was readily apparent that the results were the same with citrated plasma, heparinized plasma, isotonic saline solution, gelatin, and 6 per cent polyvinyl alcohol. In our experiments, unpooled citrated plasma caused recovery of 5 of the 10 dogs treated. Six of 10 animals survived following treatment with pooled citrated plasma. Consequently, the latter proved no better in this small series. Heparinized plasma was not more effective than the citrated, in contrast to the work of Ivy and others.⁵ This was probably owing to dif-

TABLE 1—Comparative Effectiveness of Blood Substitutes in Early Stage of Shock in Dogs

Blood Substitute	Total Number of Dogs	Number Lived	Number Died	Average Volume Transfused Cc per Kg
None	15	0	15	0
Citrated dog plasma	20	11	9	25.7
Isotonic solution of sodium chloride	20	10	10	24.3
Heparinized dog plasma	10	6	4	23.1
Gelatin, 7%	10	5	5	23.2
Pectin, 3%	10	7	3	23.6
Polyvinyl alcohol, 3%	10	3	7	25.7
Polyvinyl alcohol, 6%	8	4	4	24.4
Chi square = 3.626		P = 71%		

ference of infusion rates. In our experiments, citrated plasma was given slowly enough to allow the citrate to be metabolized and pre-

4 Bryant, E. F., Palmer, G. H., and Joseph, G. H. Nonaccumulation of Pectin Intravenously Injected into Rabbits, *Proc Soc Exper Biol & Med* **49**: 279 (Feb) 1942.
5 Ivy, A. C., Greengard, H., Stein, I. F., Ji, Grodins, F. S., and Dutton, D. F. The Effect of Various Blood Substitutes in Resuscitation After an Otherwise Fatal Hemorrhage, *Surg, Gynec & Obst* **76**: 85 (Jan) 1943.

vent death from calcium deficiency.⁶ Two dogs died while receiving plasma and before completion of the infusions. One animal received heparinized plasma, while citrated pooled plasma was given to the other dog. The results in these 2 animals were excluded. In all other animals, a well sustained elevation of blood

TABLE 2—Comparison of Effectiveness of Plasma and of Saline Solution in Later Stage of Shock in Dogs

Blood Substitute	Total Number of Dogs	Number Lived	Number Died	Average Volume Infused Cc per Kg
Citrated dog plasma	10	3	7	26.7
Isotonic solution of sodium chloride	11	3	8	23.2

pressure to approximately normal level occurred in response to plasma, and no abnormal reactions were observed.

While there was an apparent difference between the effect of 3 per cent pectin and that of 3 per cent polyvinyl alcohol, statistical analysis showed that this difference was not significant. Consequently, under our conditions of experimentation, all solutions appeared to be equally effective. Furthermore, at this level of shock, the dogs had approximately a 50 per cent chance for recovery regardless of what blood substitute was used. Since the reactions to the solutions were similar, it was interesting to note that the only properties which all solutions had in common were the volume of water and the amount of salt they contained. The colloidal material did not increase the therapeutic value of the blood substitute.

The question naturally arose as to whether plasma might prove more effective than saline solution at deeper levels of shock. The series of animals carried to a shock index of 180 provided at least a partial answer. Of 11 dogs treated with saline solution, 3 recovered completely, while 3 of 10 animals given citrated dog plasma lived. As shown in table 2, again there was no demonstrable difference in the therapeutic value of these two blood substitutes.

COMMENT

These results are opposed to those of most investigators who have tested blood substitutes.

6 (a) Sabbatani, L. Action antagoniste entre le citrate trisodique et le calcium, *Arch ital de biol* **36**: 416, 1901-1902. (b) Muirhead, E. E., Kregel, L. A., and Hill, J. M. Freezing Shock. Concentrated Plasma and Serum Therapy With and Without Amputation of the Damaged Extremity, *Arch Surg* **47**: 258 (Sept) 1943. (c) Bruneau, J., and Graham, E. A. A Caution Against Too Liberal Use of Citrated Blood in Transfusions, *ibid* **47**: 319 (Oct) 1943.

in treatment of shock. A review of the literature is not the purpose of this work. Furthermore, the excellent reviews of the subject by Scudder,⁷ Harkins,⁸ Mudd and Thalhimer⁹ and Moon¹⁰ are more than adequate. The evidence is practically overwhelming that plasma is more effective than saline solution in treating either acute hemorrhage or posthemorrhagic shock. In traumatic shock, particularly that type in which the fluid lost from the circulation is mainly pure plasma, comparisons of efficiency of blood substitutes have not yielded clean-cut results in most instances. The experimental procedures used by most workers to produce shock have usually caused death of all animals regardless of what blood substitute was given. The comparison of therapeutic value has then rested on which blood substitute would maintain an elevation of the blood pressure for a longer period. However, this did not necessarily prove that one solution was more effective than another. In terminal stages of tourniquet shock in rats, Allen¹¹ demonstrated that plasma or whole blood, but not saline solution, would revive the animals, although death subsequently resulted from shock. In certain earlier stages of shock, saline solution saved the lives of rats when plasma or whole blood failed. Until further knowledge is gained about shock, it appears to us that the one best criterion of therapeutic effectiveness is prevention of death.

One strong argument against the use of isotonic saline solution is the fact that it leaves the circulation rapidly and tends to wash some of the plasma proteins along with it, as reported by Beard, Blalock and others.¹² Isotonic saline

solution increases the blood volume for only a short period even in normal animals. Consequently, if restoration of circulating blood volume is the prime factor in treating shock, the effect of saline solution would be only evanescent. However, Rosenthal,¹³ using mice, recently showed that saline solution was more effective than serum in treating shock from both burns and tourniquets. Furthermore, the therapeutic value of serum was not changed following removal of all its proteins. The entire theory of treatment of shock by colloidal solutions has been questioned by Allen,¹⁴ who, in various types of shock, infused such large volumes of saline solution (one-fourth to one-half the body weight) that marked generalized edema occurred. Recovery from otherwise fatal shock was effected in these dogs. Katz, Friedberg and Asher¹⁵ likewise have obtained excellent results with saline solution in early treatment of shock caused by venous occlusion of the hindlegs of dogs. These findings tend to cast doubt on the concept that the fluid administered must stay in the blood vessels if it is to be effective in treating all types of shock.

The comparison of our results with those of others is obviously difficult because of difference of experimental conditions. In addition there is no intention to infer that similar results would hold true in therapy of traumatic shock in human beings. Clinicians generally seem well agreed that plasma is more effective than saline solution in all kinds of shock. It is interesting to note, however, the decidedly beneficial results

7 Scudder, J. *Shock: Blood Studies as a Guide to Therapy*, Philadelphia, J. B. Lippincott Company, 1940.

8 Harkins, H. N. Recent Advances in the Study and Management of Traumatic Shock, *Surgery* **9** 231 (Feb.), 447 (March), 607 (April) 1941.

9 Mudd, S., and Thalhimer, W. *Blood Substitutes and Blood Transfusion*, Springfield, Ill., Charles C. Thomas, Publisher, 1942.

10 Moon, V. H. *Shock: Its Dynamics, Occurrence and Management*, Philadelphia, Lea & Febiger, 1942.

11 Allen, F. M. Physical and Toxic Factors in Shock, *Arch. Surg.* **38** 155 (Jan.) 1939.

12 (a) Beard, J. W., and Blalock, A. Intravenous Injections: A Study of the Composition of the Blood During Continuous Trauma to the Intestines When No Fluid Is Injected and When Fluid Is Injected Continuously, *J. Clin. Investigation* **11** 249 (March) 1932. (b) Blalock, A., Beard, J. W., and Thuss, C. Intravenous Injections: A Study of the Effects on the Composition of the Blood of the Injection of Various Fluids into Dogs with Normal and with Low Blood Pressures, *ibid.* **11** 267 (March) 1932. (c) Beard, J. W., Wilson, H., Weinstein, B. M., and Blalock, A. A Study of the Effects of Hemorrhage, Trauma, Histamine and Spinal Anesthesia on the Composition of the Blood When No Fluids Are Injected and When Fluids

Are Introduced Intravenously, *ibid.* **11** 291 (March) 1932. (d) Blalock, A., and Beard, J. W. The Effects on the Composition of the Blood of the Subcutaneous Injection of Normal Salt Solution into Normal Dogs and into Dogs Subjected to Intestinal Trauma, Graded Hemorrhages and Histamine Injection, *ibid.* **11** 311 (March) 1932. (e) Beard, J. W., Wilson, H., and Blalock, A. Effects on Composition of Blood of Physiologic Solution of Sodium Chloride When Introduced by Intraperitoneal Injection and by Stomach Tube in the Presence of Low Blood Pressure, *Arch. Surg.* **26** 122 (Jan.) 1933.

13 Rosenthal, S. M. (a) Experimental Chemotherapy of Burns and Shock. III. Effects of Systemic Therapy on Early Mortality, *Pub. Health Rep.* **58** 513 (March 26) 1943. (b) IV. Production of Traumatic Shock in Mice, *ibid.* **58** 1429 (Sept. 24) 1943. (c) V. Therapy with Mouse Serum and Sodium Salts, *ibid.* **58** 1432 (Sept. 24) 1943.

14 Allen, F. M. Theory and Therapy of Shock: Varied Fluid Injections, *Am. J. Surg.* **62** 89 (Oct.) 1943.

15 Katz, L., Friedberg, L., and Asher, R. Efficacy of Isotonic Sodium Chloride and Glucose Solutions in Preventing Shock Following Venous Occlusion of a Limb in the Dog, *Am. J. Physiol.* **140** 5 (Oct.) 1943.

of isotonic sodium lactate used orally to treat 35 severely burned patients (Fox¹⁶) Furthermore, recent investigations tend to agree that iso-osmotic serum is more effective therapeutically than concentrated serum in shock from both burns¹³ and hemorrhage¹⁷ On theoretic grounds, concentrated serum should be at least as efficient because of its greater colloidal content However, this raises the question of how much water may be safely removed from the extracellular and intracellular fluid MacFee and Baldrige¹⁸ believed that dehydration was an extremely influential factor contributing to shock They recommended large volumes of saline solution for treating shock and condemned acacia on the basis that it holds water in the blood vessels Warren, Merrill and Stead,¹⁹ in a recent study, showed that the quantity and pressure of the extracellular fluid were important in determining the size of the plasma volume A marked decrease in plasma protein was compensated by a marked increase of extracellular fluid pressure

16 Rosenthal,^{13c} p 1435

17 (a) Levinson, S O , Weston, R E , Janota, M , and Necheles, H The Effects of Concentrated Serum in Contrast to Iso-Osmotic Plasma upon Normal and Dehydrated Dogs in Shock, *Surgery* **12** 878 (Dec) 1942 (b) Necheles, H , Levinson, S O , Janota, M , Weston, R E , and Weissman, V Studies on the Therapy of Hemorrhagic Shock I The Effects of Iso-Osmotic and Concentrated Serum and Plasma in Normal Dogs, *Surg, Gynec & Obst* **77** 337 (Oct) 1943 (c) Levinson, S O , Janota, M , Weston, R E , and Necheles, H Studies on the Therapy of Hemorrhagic Shock II The Effects of Iso-Osmotic and of Concentrated Serum and Plasma in Dehydrated Dogs, *ibid* **77** 475 (Nov) 1943

18 MacFee, W F , and Baldrige, R R (a) Post-Operative Shock and Shock-Like Conditions Treatment by Infusion in Large Volume, *Ann Surg* **91** 329 (March) 1930, (b) Physiological Considerations Related to the Infusion Treatment of Shock, *ibid* **100** 266 (Aug) 1934

19 Warren, J V , Merrill, A J , and Stead, E A , Jr The Role of the Extracellular Fluid in the Maintenance of a Normal Plasma Volume, *J Clin Investigation* **22** 635 (Sept) 1943

The exact action of isotonic saline solution in combating shock in our experiments was not determined There has been some speculation by authors recently, based on known actions of sodium chloride Rosenthal¹³ demonstrated conclusively in his animals that the therapeutic action was due entirely to the sodium ion In addition, the efficiency of sodium was decreased or neutralized by potassium Other possibilities exist such as the dilator action of sodium chloride on blood vessels²⁰ However, no proof of the exact mode of action of isotonic solution in shock has yet been presented

SUMMARY

The comparative therapeutic values of a number of blood substitutes were studied in venous tourniquet shock of dogs The procedure was controllable, so that each animal was carried to a predetermined level of shock before therapy was instituted One series of animals was studied in early shock and a second series in shock of more severe degree Untreated animals always died The blood substitutes tested were citrated dog plasma, heparinized dog plasma, saline solutions of gelatin, pectin and polyvinyl alcohol, and isotonic saline solution All of these solutions were tested in early shock In the more severe shock, citrated dog plasma and isotonic saline solutions alone were compared In both series, no difference in effectiveness could be demonstrated between any of these solutions It appeared that in this type of shock water or sodium chloride or a combination of the two was the effective therapeutic agent, while the colloidal substances did not add to or detract from the value of these blood substitutes Since this investigation was limited to shock resulting from venous tourniquets in dogs, we do not imply that saline solution would be as effective in treating other varieties of shock in animals or in man

20 Katz, L N , and Lindner, E The Action of Excess Na, Ca and K on the Coronary Vessels, *Am J Physiol* **124** 155 (Oct) 1938

GIANT NEVUS OF THE THIGH SUCCESSFULLY TREATED BY COMPLETE EXCISION AND PRIMARY GRAFTING

KENNETH L. PICKRELL, M.D., AND RICHARD C. CLAY, M.D.*
BALTIMORE

Giant moles or nevi, while not a medical rarity, are uncommon. While there is hardly any one who does not have several moles on his body, those few unfortunate persons who have large areas of cutaneous surface occupied by enormous disfiguring nevi live under a real cosmetic handicap. That such cases are not exceedingly rare is evidenced by the rather voluminous literature dealing with them. The majority, however, are reported as medical curiosities since treatment has usually been beyond the scope of ordinary means. As far as we are aware, the mole in the present case is the largest that has ever been excised and the defect closed by grafts, in either single or multiple stages.

Admittedly the various giant nevi reported in the literature have not been histologically uniform. Pack and Sunderland¹ described 4 personal and 156 bibliographic cases of what they termed *nevus unius lateris*, the criteria for which were verrucous or papillary form, linear configuration, unilaterality and extensiveness. These had been assigned thirty-nine different names in the literature. The authors did not agree with the frequently stated theory that the lesions followed the distribution of cutaneous nerves or blood vessels. Microscopically they found that the lesions showed hyperkeratosis, distortion of epidermis and elongation of papillae. "Nevus cells are seldom, if ever, seen." As evidence that the lesions are epithelial, they pointed out that when malignancy develops in such areas it is basal cell or squamous in type.

Conway² described 2 personal and 38 bibliographic cases of bathing trunk nevus. Reuben³ had previously recorded 32 such cases, including 1 of his own. Conway pointed out that these lesions, which roughly cover the lower part of the trunk and upper part of the thighs and have a brown, hairy, verrucous appearance, occasionally

give rise to melanosarcoma. As early as 1912 Fox⁴ was able to find reports of 25 of these nevi with bathing trunk distribution on the occasion of reporting a personal case. There is a good deal of overlapping in the cases reported.

Quigley⁵ reported an interesting case of bathing trunk nevus extending to the angles of the scapulas and almost half the length of the thighs. Fishback's⁶ patient had a mole which covered the back and flanks, and he died of malignant melanoma with multiple metastases. In Bhatavadekar's⁷ case the patient had a mole covering the



Fig 1—Position and extent of the nerve nevus. Beginning in the fold of the buttock, it extends medially to involve the left side of the perineum, laterally and superiorly to the uppermost part of the thigh, and inferiorly to the lower leg.

posterior part of the neck, the interscapular region, scapula and axilla. Numerous other cases of giant moles have been described.

TREATMENT

Many kinds of treatment of these disfiguring lesions have been suggested. They have been

4 Fox, H. A Case of Extensive Pigmented and Hairy Nevus, *I A M A* 58 1190 (April 20) 1912.

5 Quigley, D. T. A Case of Enormous Pigmented Mole, *J A M A* 82 2029 (June 21) 1924.

6 Fishback, H. R. Giant Pigmented Nevus with Malignant Transformation, *Am J Cancer* 40 471 1940.

7 Bhatavadekar, D. M. An Increasing Case of Nevus. *Indian M Gaz* 60 479, 1925.

*Harvey Cushing Fellow in Surgery.

From the Department of Surgery, the Johns Hopkins Hospital and University.

1 Pack, G. T., and Sunderland, D. A. Nevus Unius Lateris, *Arch Surg* 43 341 (Sept) 1941.

2 Conway, H. Bathing Trunk Nevus, *Surgery* 6 585, 1939.

3 Reuben, M. S. Nevus Pigmentosus Pilosus. *Arch Pediat* 45 364 1928.

attacked with corrosives like nitric acid and phenol, with radium and the roentgen rays, by electrodesiccation, by arsenicals, with solid carbon dioxide and by simple curettage. The results have been variable, usually unsatisfactory and sometimes disastrous. As Reid⁸ pointed out, moles should either be completely excised or let

Roy⁹ treated a 19 year old girl who had a nevus of the right cheek, upper lip and nose by multiple stage elliptic excisions with primary closure until maximal tolerable tension of the skin was attained, and he followed this by a further excision from the cheek, and covered the defect with a "dermatopidermic" graft from the



Fig 2—A close-up view of the nevus shows the many cracks and fissures, also the long hairs growing from the upper part. The nevus measured more than 18 inches in length and 10 inches in width.

alone. Unfortunately, relatively few of the lesions under consideration here have been amenable to excision, the obvious difficulty being the closure of the extensive defect left by excision of so much integument.

8 Reid, M. R. Treatment of Pigmented Moles, *Internat Clin* 4 222, 1933.

aim. He later applied a Thiersch graft to the defect remaining after the final excision of the portion on the lip. Ultimately the nevus was excised from the nose and a single pedicle flap

9 Roy, J. N. A Case of Pigmented Nevus of the Nose with Pigmented, Hairy, and Warty Nevus of the Cheek and Lip, Multiple Autoplasty, *Cure, Canad M A J* 15 138, 1925.

from the arm was used to cover the defect. The cosmetic result was good.

Meyer¹⁰ excised a large mole covering half the scalp and measuring 20 by 8 by 15 cm and successfully closed the defect with a Thiersch graft from the thigh. Fig 1¹¹ was able to remove a large thick "neuromole," 25 by 22.5 by 4 cm, from the left temporal, parietal and occipital re-

tient was a white girl of 13 years who had a spotty, verrucous, pigmented mole covering part of the left breast, abdomen, thigh, axilla, arm and hand. First, an intramammary tumor was excised after preliminary roentgen treatment, and later the abdominal portion was excised and the defect covered with Thiersch and Reverdin grafts. A year later the portions over the chest and



Fig 3—Postoperative photographs showing the various areas (designated by numbers) from which split thickness grafts were cut with the Padgett dermatome. Eight "drums" of skin were required to cover the defect which measured 220 square inches.

gions of a 29 year old man. He chose to close the defect with two large full thickness grafts from the abdomen and thigh in order to preserve hair follicles. The result was good.

Pack and Sunderland² found 2 of their 4 cases amenable to surgical procedures. The first pa-

tient was a white girl of 13 years who had a spotty, verrucous, pigmented mole covering part of the left breast, abdomen, thigh, axilla, arm and hand. First, an intramammary tumor was excised after preliminary roentgen treatment, and later the abdominal portion was excised and the defect covered with Thiersch and Reverdin grafts. A year later the portions over the chest and

10 Meyer, H. W. Massive Congenital Fibromatous Pigmented Mole of Scalp, *Surgery* 1:616, 1937.

11 Figi, F. A. Extensive Mole of the Face and Scalp. Excision and Full Thickness Skin Graft, *Proc Staff Meet, Mayo Clin* 16:280, 1941.

The other patient was a 39 year old white man who had a papillary pigmented nevus of parts of his chest and one axilla and arm. Three excisions with primary closure were carried out; two excisions were followed by Reverdin grafts.

and one by a Thiersch graft. The lesion was completely removed, but the patient died three years later of an apparently unrelated epidermoid carcinoma of the esophagus.

We report a case in which an enormous, pigmented, hair-bearing "nerve nevus" was completely excised from the lower extremity of a child and the defect successfully covered by split-thickness grafts (figs 1 and 2).

History—A 6 year old white school boy was admitted to the Johns Hopkins Hospital on Aug 10, 1943. The

of his clothing, large horny projections would be rubbed off. Except at these times, the lesion caused no discomfort. Because of the frequent episodes of trauma, bleeding and ulceration, the child was brought to the hospital.

Examination—Physical examination showed a well developed boy of 6 years weighing 56 pounds (25.4 Kg) and measuring 58 inches (147.3 cm) in height. Examination revealed no abnormality except the specific lesion. Beginning at the fold of the left buttock and extending medially over the left side of the perineum and laterally over the uppermost part of the thigh, the greater part of the left thigh was covered by a horny, black, raised, hairy nevus which extended inferiorly as far as the



Fig 4—Close-up view of the grafted area six weeks after operation. Function of the extremity was normal. Note the reduction in size of the leg and thigh following the removal of the nevus.

child's father is said to have had a pigmented hairy nevus of the buttock, but there was no other familial or hereditary trait. At birth a rough, hairy nevus was seen to occupy most of the medial, lateral and posterior surfaces of the left thigh and upper part of the left lower leg. The lesion grew and increased in size with the child's normal growth and development, and although its borders remained unchanged, it grew noticeably in thickness, reaching almost an inch (2.5 cm) in height above the surrounding skin. On numerous occasions deep cracks or fissures developed which bled profusely and were prone to ulceration and infection. At other times, because of trauma at play or from the rubbing

middle of the lower leg. The lesion measured 19 inches (48.26 cm) in length and 10 inches (25.4 cm) in width. Numerous long black hairs grew from different parts of this nevus and from its circumference. Many small cracks or fissures were present which were secondarily infected, and the lesion had a "foul" odor. Directly over the sternum there was a flat, slightly pigmented mole the size of a half dollar.

Operation—On August 11, with the patient under ether anesthesia, the nevus was excised and grafts applied in one sitting. The mass was excised in toto with more than a half inch (1 cm) margin. The nevus

extended into the subcutaneous tissues but did not invade the fascia or muscle. The size of the defect resulting from the excision was 20 inches in length (50.8 cm) and 11 inches (27.94 cm) in width, a total area of 220 square inches (1,419.4 sq cm).

The entire posterior surface of the body had been prepared with ether, alcohol and potassium mercuric iodide, and 8 sheets of heavy split thickness skin were cut from this donor area with the Padgett dermatome (fig 3). The sheets of skin were placed on the defect in a "patchwork" manner, and were sutured to one

time all of the grafts appeared to be viable. There was no gross infection. The donor areas were healing rapidly. The donor and recipient areas were dressed with gauze impregnated with sulfadiazine, and pressure dressings were applied. When the dressings were changed on the twenty-first postoperative day it was apparent that a few small areas in the donor site would require grafting, therefore on September 9, about twenty small deep Davis grafts were taken from the interscapular region and applied to the small unhealed donor areas on the posterior surface of the trunk.



Fig 5—A, microscopic section of mole, low magnification, showing mole cells dispersed through dermis and grouped in nests. Keratinized layer of epithelium is represented by amorphous mass in surface crevice. B, higher magnification of A, showing the arrangement of the mole cells suggesting Meissner's corpuscles.

another and to the periphery. The grafts were scored in many areas to allow the escape of serum and blood. Small pieces of excess skin were replaced on the donor sites to hasten epithelization. A single layer of sulfadiazine film¹² was placed directly over the donor and recipient areas, and snug pressure dressings were applied.

Postoperative Course—The original dressings were not changed until the tenth postoperative day, at which

These healed promptly, and the child was ready for discharge six weeks after operation (discharge photograph, fig 4).

Pathologic Report—The specimen as received in the laboratory contained a large, hairy mole measuring about 19 inches in length and 10 inches in width. It had been shrunk by fixation and rolled under at the edges. Almost the entire area of the specimen was occupied by the gigantic mole, a narrow cuff of normal skin surrounding it. The surface of the mole was fissured and rough and bore numerous rather coarse hairs. The rough material on the surface was so friable that particles of it came off easily when the specimen

12 Pickrell, K. L. A Sulfanilamide Film for Use as a Surgical Dressing, *Bull. Johns Hopkins Hosp.* 71: 304, 1942.

was handled. The thickness of the excised tissue averaged 2 cm, and the under surface showed grossly normal subcutaneous tissue.

Microscopically, the most striking feature was the thick, superficial layer of amorphous material corresponding to the friable layer of the gross specimen. Beneath this there was an intact thin layer of squamous epithelium whose basal layer, especially, contained brown, granular melanin pigment. The entire epithelial surface was thrown up into tall, irregular, papillary projections. The dermis was rather loose in texture with a fibrillary appearance and contained both hair follicles and sweat glands. Distributed throughout the dermis were numerous mole cells which in the deeper layers were loosely scattered and in places aggregated to resemble Meissner's corpuscles. The mole cells were more compactly arranged in dense nests between the epithelial papillae and here contained some brown melanin. There was no suggestion of malignancy or invasiveness of either the epithelium or the mole cells.

The pathologic diagnosis was benign pigmented melanoma of nerve-nevus type. Photomicrographs of the specimen at high and low power appear in figure 5.

COMMENT

A review of the literature shows that most nevi either are present at birth or appear during the first year of life. They usually increase in size with the growth and development of the child. Of the reported cases, all occurred in the white race with two exceptions, one in a Filipino¹³ and one in a Negro¹⁴. Most authorities do not believe that heredity is a prominent factor, although in our case the patient's father also had a pigmented nevus of the buttock. While many of the nevi in the published cases showed striking pigmentation, on histologic section there was rarely increased pigmentation of the basal epithelial layer. Our case showed moderately large amounts of granular pigmentation in the basal layer. In addition, mole cells were scattered

through the dermis and in the deeper layers were compactly arranged in dense nests between the epithelial papillae, as shown in the photomicrograph (fig 5).

In the reported cases no method of treatment except surgical excision with primary closure or grafting of skin was of lasting benefit. Lesions of the trunk were most frequently transverse and those of the extremities longitudinal. In many patients, as in our own, there was a segmental distribution which at first glance seemed to coincide with nerve distribution, but on close examination in the reported cases this relationship was not always observed.

The occurrence of other malformations such as those of the skeletal or muscular systems, especially the association of epilepsy, has been interpreted by some authors as showing the relationship of nevi to the central nervous system. Although various congenital abnormalities seem to appear more frequently in persons having a nevus than in those not having one, the possibility of mere coincidence cannot be discarded.

SUMMARY

The majority of giant nevi reported in the literature are described as medical curiosities since treatment has usually been beyond the scope of ordinary means. As far as we are aware, this is the largest nevus that has been excised and the defect closed by grafting in either single or multiple stages. The patient was a 6 year old white boy with a nevus of the lower extremity measuring 19 inches in length and 10 inches in width. Excision of the nevus left a defect which measured 220 square inches. Immediately after excision it was successfully covered with eight sheets of heavy split thickness skin which were cut from the posterior surface of the trunk, a Badgett dermatome being used. The grafts healed by first intention, and the child was ready for discharge in six weeks.

13 Hasselmann, C. M. Naevus Pigmentosus Verucosus Unilateralis Zosteriformis. The First Case in a Filipino, *Jap J Dermat & Urol* 35 63, 1934, abstracted, *Arch Dermat & Syph* 31 398 (March) 1935.

14 Lindenheim, H. Zur Kenntnis der systematisierten Naevi, *Dermat Ztschr* 24 144, 1917.

A REVIEW OF UROLOGIC SURGERY

ALBERT J SCHOLL, M D
LOS ANGELES

FRANK HINMAN, M D
SAN FRANCISCO

ALEXANDER VON LICHTENBERG, M D
MEXICO, MEXICO

ALEXANDER B HEPLER, M D
SEATTLE

ROBERT GUTIERREZ, M D
NEW YORK

GERSHOM J THOMPSON, M D
ROCHESTER, MINN

EDWARD N COOK, M D
ROCHESTER, MINN

EGON WILDBOLZ, M D
BERNE, SWITZERLAND

AND
VINCENT J O'CONOR, M D
CHICAGO

KIDNEYS

Renal Ectopia—Rusche and Bray¹ state that prior to the introduction of urography renal ectopia was rarely diagnosed clinically and that in most of the reported cases the condition was discovered either at the time of operation or at necropsy. The symptoms are not purely renal but frequently simulate pelvic or intra-abdominal disease. Modern urologic methods, however, have simplified this diagnostic problem, although a common pitfall is the assumption that a composition of the urine within normal limits indicates a sound urinary tract. Certain cases of renal malposition present a strong argument against this misconception and drive home the need for urologic study in cases of obscure pelvic and abdominal symptoms.

There is no definite group of symptoms peculiar to renal ectopia. An ectopic kidney is subject to all the morbid changes which may beset its normal counterpart and is rendered even more vulnerable than a normal kidney as a consequence of its position. This is explained on the basis of impaired drainage and possible trophic defects due to its aberrant blood supply. Symptoms may appear as the result of renal pathologic changes or of pressure from crowded contiguous structures. Such symptoms often lead to a confused interpretation and a mistaken diagnosis of some pelvic or intra-abdominal condition or retroperitoneal neoplasm. On the other hand, an

ectopic kidney may not produce any symptoms, and the patient may live a normal life span without being aware of his condition.

Diagnosis is not difficult with the aid of urography, and information obtained by this means is more complete from a retrograde study than from the intravenous urogram. An ectopic kidney may lie anywhere between the third lumbar vertebra and the hollow of the sacrum, in rare cases it has been found in the thoracic cavity, it has also been known to herniate through the inguinal canal. As a rule it is smaller than average, it may be smooth or lobulated, and its shape is influenced by the surrounding structures.

Two main types of renal ectopia exist—simple and crossed, which in turn may appear in unilateral or bilateral arrangement. Simple unilateral malposition is the commonest form. In crossed ectopia the anomalous organ lies on the same side as, and below the level of, the normal kidney, and its ureter empties into the opposite side of the bladder. There is little difficulty in distinguishing between the ptosed and the ectopic kidney, since the latter is fixed in position because of a short ureter, manifests an aberrant blood supply composed of short trunks and lacks the fatty capsule. The ptosed kidney is usually freely movable if it is not bound in position by adhesions, and it always has a ureter approximating normal length. Opaque catheters in place will reveal the length and course of the ureters on roentgenologic examination.

The symptomless ectopic kidney should be left alone. If symptoms warrant, and if the condition

¹ Rusche, C F, and Bray, J L. Renal Ectopia. Report of Two Cases, J Urol 50 123-130 (Aug) 1943

of the other kidney is good and its function adequate, operative intervention should be undertaken. As the ectopic kidney is fixed in position by adhesions and numerous aberrant vessels, it does not lend itself to plastic surgery, and therefore nephrectomy is the procedure of choice. The transperitoneal route is the surgical approach recommended, because it provides easy access to the kidney, permits ligation of blood vessels as they are encountered and minimizes damage to the large vessels which may lie directly beneath the organ.

Rusche and Bray report 2 cases of unilateral ectopic kidney, giving their clinical history and recording the surgical treatment (transperitoneal nephrectomy) through motion pictures in color.

Daseler and Anson² report a case of bilateral renal ectopia in an adult man. The location of the kidneys was ilio-lumbar, the lower third of each being situated in the iliac fossa.

The right kidney was covered anteriorly by the cecum, the ascending colon and the duodenal flexure, it was crossed by several large branches of the ileocolic artery. The pelvis of the right kidney was rotated medially. Two right renal arteries were present, originating from the aorta at the level of the mesenteric arteries. Three right internal spermatic arteries occurred. Two right renal veins were present, separated by an interval of 2 cm and draining separately into the inferior vena cava.

The left kidney was normal in size, but its pelvis was situated anteriorly and measured 5 cm in length (half the total length of the organ). There was a single left renal artery, derived from the aorta. Two left internal spermatic arteries were present. Three renal veins emerged from the left renal hilus to fuse into a single pre-aortic trunk draining into the inferior vena cava.

In simple structural terms, the kidneys, the ureters and the associated blood vessels (including the aorta and the vena cava) may be said to be contained in, and supported by, a fascial envelope which is interposed between the anteriorly placed vessels (and autonomic nerves) of the digestive tube and the posteriorly situated parietal vessels, the nerves of the lumbar plexus and the lumbar musculature. Whether the kidney is normal or ectopic, the investment remains the same. Within the investing fascia the renal arteries and veins will have connection with the aorta and the vena cava or with pelvic extensions of these by vessels which course in a trans-

verse plane. The anterior and posterior relation to the retroperitoneal vessels in front and to the retrofascial nerves and muscles behind would be predictable within the limits of normal anatomical variation.

Tumor Thrombosis of the Renal Vein
McDonald and Priestley³ review data on approximately 700 cases of malignant tumor of the kidney in an effort to determine the surgical and the prognostic significance of tumor thrombosis of the renal vein. Some kidneys that had been mutilated were discarded from the series, which left 636 kidneys containing malignant neoplasm for inclusion in this study. Only that portion of the renal vein and artery with their tributaries which lay outside the renal parenchyma was examined. The presence or the absence of a malignant neoplasm in the aforementioned portion of the renal vein and artery or in the perineural lymphatics situated outside the renal parenchyma was determined, and any neoplasm found was identified, by gross and histologic methods in all cases.

In 509 of the 636 cases the renal cancer was a hypernephroma. Malignant thrombosis of the renal vein was present in 275, or 54 per cent, of the cases of hypernephroma. There was no evidence of neoplastic involvement of an artery in any of the cases of hypernephroma. In a number of instances histologic examination disclosed endarteritis of the main renal artery, occasionally with benign thrombosis, but neoplastic involvement could not be demonstrated. Involvement of the perineural lymphatics was observed in only 1 case.

The mortality rates in the first year after the patients with hypernephroma were dismissed from the hospital were as follows: 38 per cent for those in whom the renal vein was thrombotic at the time of operation and only 18 per cent for those in whom tumor thrombosis of this vein was not present. This is another indication that tumor thrombosis of the renal vein in a case of hypernephroma seriously affects the prognosis. The five year survival rate in these two groups of patients combined was 41.5 per cent. It was 55.4 per cent for those in whom tumor thrombosis of the renal vein was not encountered at operation and only 29 per cent in those in whom thrombosis was present.

A thrombotic renal vein was found in 49.8 per cent of cases in which the hypernephroma was grade 1 or 2 and in 61.9 per cent of those in which the tumor was grade 3 or 4. It is

2 Daseler, E. H., and Anson, B. J. Anatomical Relations of Ectopic Ilio-lumbar Kidneys. Bilateral in Adult, Unilateral in Fetus, *J. Urol.* 49: 789-802 (June) 1943.

3 McDonald, J. R., and Priestley, J. T. Malignant Tumors of the Kidney. Surgical and Prognostic Significance of Tumor Thrombosis of the Renal Vein. *Surg., Gynec. & Obst.* 77: 295-306 (Sept) 1943.

apparent, therefore, that even hypernephroma of low grade has a great tendency to invade the renal vein.

The incidence of tumor thrombosis according to the weights of the involved kidneys was as follows: 40.6 per cent for weights of less than 500 Gm, 58.8 per cent for those of 500 to 999 Gm, and 63.1 per cent for those of 1,000 Gm or more.

In 76 of 119 per cent of the entire series of cases of malignant tumor of the kidney, the neoplasm was a carcinoma of the renal pelvis. Involvement of the perineural lymphatics in the hilus of the kidney or tumor thrombosis of the renal vein or both were present in 34, or 44.7 per cent of the cases of carcinoma of the renal pelvis. Thrombosis of the main renal vein or of one of its smaller branches in the hilus of the kidney was present in 31 of the 34 cases. Involvement of the perineural lymphatics in the hilus of the kidney was present in 23 of the 34 cases. Tumor thrombosis of the renal vein was present in 20, or 86.9 per cent, of the 23 cases in which there was involvement of the perineural lymphatics. In 1 of the 20 cases thrombosis of the renal artery also was present.

Tumor thrombosis of the renal vein or involvement of the perineural lymphatics or both were present in 14, or 45.2 per cent, of the cases of Wilms's tumor. The perineural lymphatics were involved in 2 cases. Tumor thrombosis of the renal vein also was present in 1 of these cases. Tumor thrombosis of the renal vein or involvement of the perineural lymphatics or both apparently had little influence on the five year survival rate in the cases of Wilms's tumor.

Tumor thrombosis of the renal vein was present in 2 of the 20 cases of sarcoma of the kidney. Involvement of the perineural lymphatics was not encountered in any of these cases. Here thrombosis of the renal vein did not appear to be of prognostic significance.

A renal neoplasm should be handled as gently as possible to avoid breaking loose a possible tumor thrombus in the renal vein. It should not be compressed, pulled on or manipulated in any other manner to more than a minimal degree. As soon as possible during the operation the surgeon should identify and isolate the renal pedicle.

The wall of the vein containing a tumor thrombus may become involved by the neoplastic process. This means that the portion of the vein to which the thrombus is attached must also be removed if all tumor tissue is to be removed.

The easiest type of tumor thrombus to deal with is the one which extends for such a short distance in the renal vein that there is enough uninvolved portion of the vein for the application of clamps between the thrombus and the vena cava. Such a case does not offer any particular problem except that care always should be taken not to dislodge the thrombus and not to include any of it in the clamps. In other cases it may be found that the thrombus extends almost to the vena cava so that there is space for the application of only one clamp between the end of the thrombus and the vena cava. Under these circumstances this clamp should be applied to the renal vein and the tumor removed. Any involved portion of the renal vein distal to the clamp may then be excised, and the remaining portion may be utilized for obtaining hemostasis either by ligature or by suture. If necessary, one or more clamps may be left in place on the renal vein with safety. These are loosened in forty-eight hours and removed in seventy-two hours. Fortunately, the renal artery in cases of hypernephroma is practically never involved with tumor thrombus, and therefore the arterial blood supply to the kidney may be controlled in the usual manner.

Wilms's Tumor—Livermore⁴ presents a case of Wilms's tumor in a woman 37 years of age. In 1941, the right kidney was explored, and a perirenal abscess and a tumor mass were found. Cystoscopic and pyelographic examinations revealed a large mass continuous with the lower pole of the right kidney. This kidney with the mass was removed surgically, and the diagnosis was Wilms's embryonal tumor.

Tuberous Sclerosis—Mertz⁵ reports a case of tuberous sclerosis of the brain and renal tumor. The patient, a girl aged 3, had a congenital enlargement of the left leg and the left side of the vulva. Fulness in the upper part of the abdomen was noted, though no mass or deformity was made out. On the outer aspect of the thigh were numerous small capillary hemangiomatous areas, and the skin in this region had a slightly bluish tinge. A diagnosis of probable hemangioma of the left leg and of the vulva was made. No treatment was instituted. Six years later the patient, aged 9, entered the hospital because of convulsions, swelling of the left leg and of the vulva and presence of a mass in the upper left portion of the abdomen. There

4 Livermore, G. R. Wilms' Tumor in the Adult. Report of a Case, *Tr. Am. A. Genito-Urin. Surgeons* (1942) 35:67-71, 1943.

5 Mertz, H. O. Tuberous Sclerosis and Renal Tumor, *Tr. Am. A. Genito-Urin. Surgeons* (1942) 35:73-85, 1943.

was a cutaneous eruption over the face. The left leg was approximately one and a half times as large as the right, and a mass the size of a grapefruit was found in the upper left abdominal quadrant. A roentgenogram of the skull revealed multiple irregular areas of calcification in the calvarium on the cortical surface of the brain. A diagnosis of tuberous sclerosis with adenoma sebaceum, renal tumor on the left side and congenital angiomatous changes in the left leg and left labium majus was made. The patient was given sedation treatment for her convulsions and roentgen treatment for her renal neoplasm.

Mertz states that the three most often encountered types of neurocutaneous syndrome that may be accompanied by a renal tumor are Recklinghausen's neurofibromatosis, Bourneville's tuberous sclerosis and Landau's type of von Hippel's disease a form of angiomatosis. Each is due to a congenital malformation occurring in the brain, the skin, the heart, the eyes, the kidneys, the bones or occasionally other viscera. The pathologic changes and the clinical expression are distinctive and definite in each disease.

Tuberous sclerosis is a chronic disease which particularly affects the brain, the eyes and the skin but which to a lesser degree involves the mesoderm, resulting in formation of an embryonic tumor in the heart, the kidneys or other viscera. Invasion of the brain results in varying degrees of mental defect and convulsions. The cutaneous lesion, adenoma sebaceum, is present on the cheeks and the nose. It is most characteristic in its butterfly distribution and is usually most evident in the nasolabial folds. The ocular changes consist of flat tumors on the retinas. Typical changes occur in the heart and the kidneys and less frequently in other viscera.

There is no treatment known for tuberous sclerosis. The disease is progressive. It is observed sometimes in adulthood but occurs most often in childhood. Most patients die between the fifth and the fifteenth year of age, and death results most often from cachexia, pulmonary disease or status epilepticus.

The characteristic renal lesion in tuberous sclerosis is a tumor formation. While it was thought at first that the renal changes were accidental and did not have any relation to the lesion of the brain, it was soon suggested that they had more than a casual relation and that the hypertrophic nodular gliosis in the brain and the tumor formation in the kidney were but two expressions of one and the same disease.

Most of those making complete necropsy reports on patients with tuberous sclerosis have noted the presence of renal tumors, yet occasionally an instance of tuberous sclerosis without renal changes has been shown.

The renal changes may be bilateral. The relative frequency of both kidneys being involved is difficult to determine as reference to the renal lesion in necropsy reports is most often limited and incomplete. In 16 of the 19 cases of renal tumor in the Fowler and Dickson series, both kidneys were affected. In the series of 42 patients with tuberous sclerosis and tumor of the kidney whose records Mertz has collected from the literature the disease was bilateral in 34 and unilateral in 2.

The characteristic lesion in the kidney is a cystic or a solid tumor. While the two types of tumor may occur independently, in most instances careful study will demonstrate that both types are present. The tumors are primarily cortical in location and frequently they extend into the medulla but in doing so there is no invasion of the deeper structures as in cancerous renal tumors. Almost invariably the tumors are multiple and many definitely distinct tumors are present with no appreciable tendency toward the formation of one large tumor mass.

Hydronephrosis—Henline and Menning⁶ in discussing hydronephrosis due to ureteropelvic obstruction state that the diagnosis of ureteropelvic obstruction should be made before operation by a ten minute delayed roentgenogram.

The exact cause of the obstruction must be sought and corrected at the operating table.

Among urologists and roentgenologists the opinion still prevails that aberrant vessels are the primary cause of most ureteropelvic obstructions. In Henline and Menning's cases the most common cause of obstruction was intrinsic stenosis. Stenosis and aberrant vessels frequently coexist, and at operation careful study of the ureteropelvic junction may be required to determine the primary cause of the obstruction. When stenosis and aberrant vessels coexist, both must be corrected to establish adequate drainage.

The success of any plastic operation on the ureteropelvic junction depends as much on prolonged nephrostomy drainage and ureteral splinting as on the surgical procedure employed. A Malecot catheter serves well for prolonged nephrostomy drainage, and a soft rubber catheter

6 Henline, R. B., and Menning, J. H. Management of Hydronephrosis Due to Ureteropelvic Obstruction. Preliminary Report, *J. Urol.* 50:1-24 (July) 1943.

which fits snugly into the ureter has proved to be a satisfactory ureteral splint

In cases in which this method of prolonged drainage was followed, the immediate results with both Y-plasty and end to end anastomosis have been gratifying

Cyst—Braasch⁷ states that recently he has observed in a number of patients unusual renal cysts which have been more or less difficult to classify. He refers to cysts situated in the renal cortex adjacent to a calyx. These cysts apparently have their origin in the tip of the calyx and in many instances should be considered cystic dilatations of the calyx. They often start with the formation of a small stone in the tip of the calyx which obstructs the tubules leading into it, causing cyst formation. Chronic pyelonephritis may produce constriction of the infundibulum leading to a calyx with secondary formation of a cyst. In no sense of the word can these cysts be called simple or solitary renal cysts. The best term to describe them has been offered by Quimby, who suggested the name "pyelogenic cysts." As a rule, they are smaller than the "simple" cysts usually observed. Renal cysts occasionally are observed that were primary cortical or "simple" cysts situated adjacent to the pelvis which ruptured into a calyx. It may then be difficult to distinguish them from pyelogenic cysts.

The diagnosis is made possible by urography. As a result of routine employment of this procedure in recent years the lesion is recognized much oftener than formerly. In some cases the cysts are not visualized in the excretory urogram and their presence may be determined only by a retrograde pyelogram. In other cases they are visualized only in the excretory urogram. In some instances the original connection with the pelvis has been sealed off so that for all practical purposes they become cortical cysts. A calculus, usually small, is present in many of these cases. The question may arise whether the stone is a secondary formation rather than a primary etiologic factor. If multiple small stones should be present in the cyst, they would seem to be definitely secondary.

Persistent or recurring urinary infection is usually the predominant clinical evidence in cases of pyelogenic cyst. Hematuria is sometimes observed. Acute pain usually is absent. The accidental discovery of the cysts in the course of routine urography is not unusual.

In the absence of secondary complications pyelogenic cysts may be left untreated, with

subsequent observation. When persistent secondary infection or a stone is present, complete excision usually is indicated. If a cyst is large enough, amputation of the affected renal pole may be advisable.

In a recent review of a series of 163 cases of simple renal cyst in which operation was performed at the Mayo Clinic, Braasch made the following classification of renal cysts, which for his purposes has proved to be practical: (1) retention or inflammatory cysts (usually of little or no clinical significance), (2) simple cysts (single, multiple, multilocular or hemorrhagic), (3) pyelogenic cysts, (4) peripelvic cysts, (5) cysts secondary to renal pathologic change (calculus, hypernephroma, tuberculosis, pyelonephritis, hematoma or echinococcus), (6) polycystic kidneys.

Nephritis—Lobo Onell and Diaz Muñoz⁸ state that the operation of renal decapsulation and denervation in acute glomerulonephritis is innocuous and helpful in halting the progress of the disease in its acute form. Careful judgment is required so that operation shall not be performed in cases in which the condition is amenable to medical treatment. On the other hand, procrastination may lead to irreversible parenchymal changes. Operation should be done at the crucial moment before the disease becomes chronic.

The most striking results were seen in cases of subacute glomerulonephritis.

In cases in which the disease had reached the subchronic phase, the results were variable. While in some instances they were encouraging, in others no appreciable benefit was derived.

As to the chronic form, careful discrimination must be used in the selection of cases. Operation is indicated in acute exacerbations of chronic nephritis and when there are pain and hematuria.

In the vascular forms, in which hypertension is the chief symptom, decapsulation and denervation must be done before the majority of the arterioles are obstructed, so that the full benefit of the resultant vasodilatation can still be had.

Hypertension—Patton, Page and Ogden⁹ review the reported clinical cases of hypertension and unilateral renal disease in which nephrectomy was done. In more than half of these cases either the blood pressure remained at the

7 Braasch, W. F. Pyelogenic Renal Cyst, *Urol. Corres. Club Letter* 10: 67-68 (July 19) 1943.

8 Lobo Onell, C., and Diaz Muñoz, I. Results of Surgical Treatment of Diffuse Glomerular Nephritis, *J. Urol.* 50: 34-39 (July) 1943.

9 Patton, H. S., Page, E. W., and Ogden, E. The Results of Nephrectomy on Experimental Renal Hypertension, *Surg., Gynec. & Obst.* 76: 493-497 (April) 1943.

same level or it continued to rise after the operation

This problem was studied in rats in order to determine the factors which influence the success or the failure of nephrectomy in curing hypertension. Permanent high blood pressure was produced by obstructing the blood supply to one kidney, and this kidney then was removed after varying intervals. Corresponding to the results in man, half of the rats did not have any lowering of the blood pressure and only 20 to 30 per cent of the animals were cured of hypertension. In the animals that had residual hypertension, albuminuria persisted, and a histologic study of the remaining kidney revealed numerous vascular changes similar to those observed in the kidneys of human beings with hypertension and apparently accounting for the continued maintenance of the high blood pressure. If the affected kidney had become completely devoid of a blood supply, its removal was a useless procedure. The greatest success following nephrectomy was in those cases in which hypertension was of short duration, and within the limits of the experiments the severity of the hypertension was not of importance in determining the end result.

Aneurysm—Lowsley and Cannon¹⁰ state that 75 cases of aneurysm of the renal artery have been reported to date, including the case presented in their paper.

A congenital defect in the wall of the renal artery, particularly at its bifurcation, is a hypothetical factor in the causation of aneurysm. It is questionable whether trauma per se produces renal aneurysm.

In only 12 of the 75 reported cases was the condition suspected prior to operation or death.

True aneurysm is usually asymptomatic. A few patients have complained of pain in the flank. The cardinal symptoms of false aneurysm are hematuria, pain and tumefaction in the flank. The pathognomonic signs—pulsation and a systolic bruit—have been present in 7 cases. The presence in the roentgenogram of a ringlike shadow, with a dense periphery disrupted in one portion and a rarefaction of the center, in the kidney or the hilar region, is suggestive of a renal aneurysm.

The treatment is surgical. According to the literature, every patient presenting symptoms on whom operation was not performed died. Of the 29 patients subjected to nephrectomy, 26 survived. Of 37 patients who underwent opera-

tion, 8 died—an operative mortality rate of 21 per cent.

Actinomyces—Cohen,¹¹ in a discussion of actinomyces of the kidney, states that Actinomyces may gain entrance into the body through injuries, such as abrasions or cuts, by being ingested with food or by being inhaled in the form of spores. Isolated infection of the kidney probably occurs as a result of hematogenous spread.

A preoperative diagnosis of renal actinomyces can be established only by finding the ray fungus in the urine. This is often difficult because Actinomyces may not have a typical form but may resemble cocci and ordinary bacteria. Cultures may give positive proof, but the organism is very slow growing, often requiring several weeks of cultivation. Cultures made by ordinary methods do not reveal the presence of the ray fungus. There are usually no localizing signs or symptoms. Both the retrograde and the excretory pyelograms are without distinctive features.

Cohen reports the case of a man aged 44 years, who complained of pain in the left loin. The patient had had one attack of painless hematuria. Excretory urography showed a calculus in the left ureter, with left hydronephrosis and hydronephrosis. Later cystoscopic examination revealed a scar in the region of the left ureteral orifice. Following this, a stone was removed by left ureterolithotomy. After operation the patient had some fever and tenderness in the left costovertebral angle. A retrograde pyelogram showed that the hydronephrosis had disappeared. A diagnosis was made of cortical abscesses of the kidney. An exploratory operation was performed. The kidney was found to be considerably enlarged, with a greatly thickened capsule, and through the latter could be seen tiny yellowish abscesses. Examination by a pathologist of a section taken from the kidney revealed actinomyces. Following operation, the patient was given potassium iodide for several months, and he made a good operative recovery.

Renal Operation for Drainage of Ascitic Fluid—Ferguson¹² reports a case in which the pelvis of one kidney was anastomosed to the peritoneum in a case of ascites. The patient was a man aged 38 years, for whom a diagnosis of cirrhosis of the liver, ascites and nephritis was made. The usual treatment, such as tapping and the admin-

11 Cohen, D. L. Primary Actinomyces of the Kidney. Case Report, *J Urol* 50:29-33 (July) 1943.

12 Ferguson, C. Ascites. An Operation for Its Relief, a Case Report, *J Urol* 50:164-168 (Aug) 1943.

10 Lowsley, O. S., and Cannon, E. M. Aneurysm of the Renal Artery, *J. A. M. A.* 121:1137-1143 (April 3) 1943.

istration of mercurial drugs, had been tried with only temporary relief. Excision of the right kidney and anastomosis of its pelvis to the peritoneum were performed. This operation was done with the purpose of permanently draining the peritoneal cavity by way of the right ureter. The patient's condition was satisfactory following operation. The vesical output averaged from 1,300 to 1,500 cc in twenty-four hours. After a necessary modification was carried out, no further ascites occurred. The patient was in good health one year after operation.

ADRENAL GLANDS

Cortical Tumors—Howze¹³ reports a case of bilateral tumor of the adrenal cortex. The patient was a man aged 51 years, whose urogram showed a mass in the right lumbar region and a deformity of the right renal pelvis. On physical examination the mass was found to be multiple, about the size of a grapefruit. A diagnosis of renal tumor on the right side was made. The patient died somewhat later, and at necropsy a tumor of each adrenal gland was found, together with a small metastatic tumor in the myocardium. Both adrenal glands were greatly enlarged, the normal pattern being almost completely replaced by lobulated masses of yellowish tissue with pink streaking, the latter radiating from the central regions toward the outer edges. On the right side this tissue was seen to continue into the hilus of the kidney and to replace in an expansive development practically the entire kidney, leaving only an incomplete narrow shell of essentially normal renal pattern. The left kidney was not involved in the neoplastic process. Microscopic examination indicated that the growth of the adrenal cortex was a carcinoma.

In a review of the literature on adrenal tumors from 1850 to the present time, Howze found reports of 66 bilateral tumors of various types. There are 2 specimens in the Army Medical Museum not yet reported, which make a total of 69. Forty-five of this group appear to be true cortical tumors arising from the cells of the adrenal cortex and are cytologically adenomas and carcinomas. Six bilateral paragangliomas are reported. The remainder are classified as sarcomas of various types, melanomas, a cavernous angioma and a retroperitoneal cyst of undetermined character. In all cases the diagnosis was made at necropsy except in the case of the retroperitoneal cyst, the origin of which

was doubtful. The youngest of the patients was a boy 4 days old, and his tumors were described as adenomatous hypertrophy. The oldest patient in whom necropsy revealed true cortical tumors was a man aged 68 years. A majority of the patients were in the fourth and fifth decades of life. Among the patients there were 36 men and 25 women, in 5 cases the sex was not mentioned. The diagnosis was not made in a single instance during life.

Cahill,¹⁴ in discussing Howze's paper on bilateral tumor of the adrenal cortex, states that it is difficult at times to distinguish adrenal tumors microscopically from renal tumors, and some of the sections shown by Howze look like hypernephroma. The differentiation must be done chemically, simply because the adrenal cell and the renal cell are chemically two different things, and long differential chemical staining of cells is the only way to recognize them. Consequently, it is sometimes difficult to determine whether a tumor is of renal origin with metastasis into the opposite adrenal gland. Cahill states that he would not be satisfied with the diagnosis unless pathologic and chemical examinations were made as far as possible to see whether the cells in the tumor are renal cells or adrenal cells. Howze's patient died of acute chronic adrenal depletion (chronic Addison's disease), pigmentation does not necessarily occur in chronic Addison's disease, because apparently the various syndromes of this disease express not only the loss of hormones but the loss of vitamins which goes with depletion of an adrenal gland.

Hyman and Mencher¹⁵ discuss pheochromocytoma of the adrenal gland and report 4 cases. Thirty-five cases of pheochromocytoma for which operation was performed have been reported in the world's literature. In the combined series there were 5 postoperative deaths. Another death occurred two years after operation, of metastasis. That is the only case of malignant tumor reported in the whole group. Pheochromocytoma did not involve either adrenal gland in 4 cases, and occurred more often among women than among men.

The symptom complex is dependent on the discharge of epinephrine or of an epinephrine-like substance into the general circulation. The symptoms produced during spontaneous and

¹³ Howze, C. P. Bilateral Adrenal Cortical Tumors. Report of a Case Simulating Renal Neoplasm, *Tr Am A Genito-Urin Surgeons* (1942) **35** 21-39, 1943.

¹⁴ Cahill, G. F., in discussion on papers by Jeck and Orkin, Shupe, Howze¹³ and McKenna, Kiefer and Bronstein,¹⁰ *Tr Am A Genito-Urin Surgeons* (1942) **35** 63-64, 1943.

¹⁵ Hyman, A., and Mencher, W. H. Pheochromocytoma of the Adrenal Gland, *J Urol* **49** 755-771 (June) 1943.

induced attacks are more or less similar, differing only in severity. A typical history reveals that the patient complains of pounding headache, nausea, dyspnea, orthopnea, palpitation, blanching of peripheral portions of the body, paresthesias, abdominal cramps, vomiting, precordial throbbing and marked weakness. The attacks last for variable periods from minutes to hours, during which time the patient may be in a state of shock. The attacks usually terminate with flushing of the blanched areas, marked perspiration and weakness. During an attack death may occur from shock, pulmonary edema, failure of the left side of the heart or coronary disease or with cerebral manifestations. If surgical treatment is not given, eventually arteriolar sclerosis results because of unchecked vascular tension. The hypertension which then results becomes fixed.

The attacks may occur spontaneously, or they may be induced by any mechanism which calls forth a discharge of epinephrine (pressor response). These causative factors include emotional upset, fear, anger, slight trauma, change of posture and other conditions. Some patients have succumbed without apparent cause after a trivial operation.

Peripheral vasoconstriction is usually marked and manifests itself in several ways. The blood pressure may rise to more than 300 mm of mercury systolic, with the diastolic pressure at levels of more than 100 mm, only slightly elevated. At the time of the hypertensive phase the pulse is markedly thin or impalpable.

If the attack has lasted for a long period, the patient may be in a state of shock, which is dependent on the prolonged massive introduction of epinephrine into the circulation.

The urine usually is decreased in volume and contains albumin, erythrocytes and casts, glycosuria may be present. Between attacks the urine may be normal.

Pyelography may show a compression of the upper pole of the kidney if the tumor is large. If the tumor is small, there may be no indication from the pyelographic studies that a tumor exists in the region of the adrenal gland. For this type of case perirenal insufflation is essential and easily demonstrates and localizes the tumor.

Medullary Tumors—Tumor of the adrenal medulla must be differentiated from hyperthyroidism, coronary occlusion and ordinary hypertension.

In the management of patients with tumor of the adrenal medulla, careful preoperative preparation is of paramount importance. Emotional excitement should be avoided. Knowledge of the

operation should be withheld from the patient, and sedation should be adequate. The use of solution of trichloroethanol U S P as the basal anesthetic affords opportunity to avoid the excitation which other anesthetic procedures may cause. Extract of adrenal cortex, as well as epinephrine, has been recommended in the management of these patients because of the sudden release from a state of high titer of circulating epinephrine following the operation and because of the possibility of temporary adrenal cortical insufficiency which the loss of adrenal cortical tissue might cause. Furthermore, it has been shown that the administration of an extract of adrenal cortex is of benefit when the circulatory collapse of epinephrine shock is produced. Desoxycorticosterone and salt should also be employed preoperatively, but a word of caution is necessary in regard to this medication. Overdosage should be avoided since it leads to pulmonary edema, to which a patient may succumb.

Preparation is made at the operation for frequent determinations of blood pressure by the anesthetist. Since excessive handling of the tumor causes discharge of large amounts of epinephrine into the circulation, adequate exposure of the area and gentleness of technic are essential. When the tumor is small, lumbar incision with excision of the twelfth rib and if necessary the eleventh rib is advised. However, when the tumor is huge, the transperitoneal approach is more advisable than the lumbar approach. In the lumbar incision, the posterior portion of the usual renal incision is extended upward to parallel the spine to the eleventh rib. After excision of the twelfth rib, the kidney is exposed and packed away toward the iliac fossa. The tumor is located, and a decision is then made as to whether to excise the eleventh rib. Care is taken not to injure the pleura. After being located the tumor is removed with as little handling as possible. Striking rises of blood pressure may be noted as soon as the tumor is manipulated. Following the removal of the tumor, the blood pressure may fall precipitously. This event calls for a close watch over the patient. In much more than half of the reported cases the patient has suffered from shock during or immediately after the operation. Intravenous infusion, intravenous injection of solution of epinephrine hydrochloride U S P and intramuscular administration of a suspension of epinephrine in oil are indicated for any immediate collapse. Extract of adrenal cortex and desoxycorticosterone are valuable agents in therapy following the epinephrine regimen.

The postoperative care consists of the continuation of the regimen started in the preoperative period. After the shock has been combated successfully, convalescence is uneventful. Further spontaneous attacks cease, and efforts to induce the paroxysms are no longer successful. The results of studies of blood and urine become normal. The response to the various pressor tests likewise does not show any deviation from the normal.

Of the 4 patients whose cases are presented, 3 were women and the fourth was a man. All the tumors were removed successfully, and all the patients made uneventful recoveries. A long period of follow-up reveals that the patients are in excellent health and that no further attacks have occurred.

Cahill,¹⁶ in discussing Hyman and Mencher's article on pheochromocytoma of the adrenal gland, states that the patients present a hormonal or paroxysmal type of hypertension, which is distinct from the continuous essential type, which most likely is due to some amino acid. In both of these types of hypertension, correction is necessary before the patient is permanently injured.

Pheochromocytomas are usually benign and occur mostly in adults. In some cases of major hysteria there are attacks which resemble the hormonal crises occurring with pheochromocytoma.

When the classic symptoms are present, the first diagnostic step is to prove the presence of excess hormone. The next step is to prove its source, which has been done best by perirenal insufflation of air. After the tumor has been located, its removal is necessary. The anesthetic agent of choice is solution of tribromoethanol. U S P

In operations on adrenal tumors, it is best to remove a malignant cortical tumor through a transperitoneal approach. For a benign tumor, such as pheochromocytoma, the flank incision is adequate. Ligation of the blood supply should precede the handling of the tumor.

It has been the experience of most surgeons that the blood pressure remains low for some time after the removal of a pheochromocytoma, but if the patient survives the operation, cure usually follows, in other words, hypertension due to this tumor is a type of hypertension that can be cured.

MacKenzie¹⁷ states that he has seen 4 patients who had pheochromocytoma of the adrenal gland.

but that his results have been not quite so satisfactory as those of Hyman and Mencher, for 1 patient died.

He discusses a case in which he operated five years ago. The patient was a man of 29 years. There were several things which were interesting about this patient. One was that he always had a sudden spasmodic rise of blood pressure when pressure was applied in the region of the left kidney, but none when pressure was applied over the right kidney. He was admitted to the neurologic service with a tentative diagnosis of tumor of the brain. At operation, the left side was explored and found to be normal, then, on the right side, a large tumor was found. When the patient was dismissed, his blood pressure was 110 systolic and 70 diastolic. From then on, the highest pressure reading was reported to be 120 systolic and 80 diastolic. About four months ago, while taking his gymnastic exercises in the morning, bending forward, he got one of those attacks, as he said, "not very severe, but there is no question but that the attack is the same as experienced before operation." Following that, he had five or six attacks before returning for treatment. None of these attacks was as severe as the previous ones, but they were definite. He entered the hospital about a month ago and was able to produce the attacks by his gymnastic exercises, but pressure in the renal regions produced no change. Exposure of both adrenal glands at operation revealed them to be normal. While the patient was on the operating table, MacKenzie tried flexing the patient's body by bending the thighs against the abdomen. This was followed by a rise of the blood pressure to 282 systolic and 166 diastolic.

Mencher¹⁸ states that pheochromocytoma produces a type of hypertension paroxysmal in nature and remediable by surgical treatment. It is important that a diagnosis be made and surgical treatment rendered before the hypertension becomes fixed.

Pseudohermaphroditism and Adrenal Disease—McKenna, Kiefer and Bronstein¹⁹ discuss pseudohermaphroditism in relation to the adrogenital syndrome. They present 2 cases in which an operation was done and a third case in which the diagnosis was made clinically but no surgical treatment was carried out.

The first case was that of a girl aged 14 years. The patient always had known that she had an

¹⁶ Cahill, G. F., in discussion on Hyman and Mencher,¹⁵ p. 772.

¹⁷ MacKenzie, D. W., in discussion on Hyman and Mencher,¹⁵ pp. 772-773.

¹⁸ Mencher, W. H., in discussion on Hyman and Mencher,¹⁵ pp. 775-776.

¹⁹ McKenna, C. M., Kiefer, J. H., and Bronstein, I. P. Pseudohermaphroditism Due to Hyperactivity of the Adrenal Cortex, *Tr. Am. A. Genito-Urin. Surgeons* (1942) **35**: 41-58, 1943.

enlarged clitoris, which recently had been enlarging rapidly. In general, she was a muscular child, having more male characteristics than female. There was a marked growth of suprapubic hair with the male type of escutcheon extending up to the umbilicus. There was a rather large phallus, about 2 cm in diameter and about 4 cm long, of the hypospadiac type with ventral curvature. At the base of this phallus was what at first seemed to be a urethra, however, on closer examination a vaginal orifice was seen, on spreading this the urethral orifice could be seen immediately inside. It was possible to do a vaginal examination with one finger, and the small, apparently normal uterus was palpable. No masses were found in the pelvis. Cystoscopic examination revealed a normal bladder and urethra. On abdominal exploration a normal uterus was found, the ovaries appeared undeveloped. At a second operation, both adrenal glands were exposed. The right adrenal gland was somewhat enlarged, and a part of it was removed. Later the clitoris was amputated and the perineum opened more widely to establish a more normal female condition of the genitalia. Five months later the patient was in good general health, the body contours were more feminine, and there was beginning development of the breasts.

The second case was that of a girl aged 4 years. The genitalia had been noticed to be abnormal at birth but were predominantly female. Examination revealed a large phallus, 2 cm in diameter and 4 cm in length. There was a perineal urethral meatus, and no division of this canal could be seen when the meatus was spread. An abdominal exploratory operation was carried out. The uterus and the ovaries were normal but small. Injection of air into the perirenal space on the left side showed the left adrenal gland to be approximately 20 by 30 mm in outline, the right adrenal gland was not outlined. The right adrenal gland was then exposed surgically and three fourths of it resected. Examination of the sections led to a diagnosis of cortical adenoma of the adrenal gland and diffuse and focal pseudonodular hyperplasia of a disordered adrenal cortex.

URETER

Calculus—Beach²⁰ states that ureteral calculus is common in the Sacramento Valley, in California.

Watchful waiting is advisable, since spontaneous expulsion of the calculus is fairly frequent.

²⁰ Beach, E. W. Ureteral Calculus. Its Management, California & West Med 58 113-118 (March) 1943.

Error in judgment, or leaning too far toward conservatism, however, may result in increased morbidity and perhaps otherwise avoidable mortality.

Beach's expectant treatment consists of insertions of a soft indwelling ureteral catheter, left in situ for twenty-four to forty-eight hours, under aseptic conditions. On withdrawal of the catheter, sterile olive oil is injected, and prostigmine methylsulfate is given hypodermically, with the patient ambulant. An aid to securing ureteral relaxation for the removal of large stones is found in deproteinized pancreatic extract, administered just before instrumentation. Metal forceps and metal-tipped stone dislodgers do not have any place in instrumentation within a ureter weakened by stone, as demonstrated in 3 cases observed by the author, in which perforation occurred.

Failure to respond to a reasonable trial of manipulative measures should be followed by open operation.

About 75 per cent of ureteral stones reach the pievesical spindle. If ureteral meatotomy is necessary, the use of scissors or a cold knife is preferable to fulguration.

Beach warns that the position of the stone must be rechecked immediately before operation.

Carcinoma—Scott²¹ reports 2 cases of carcinoma of the ureter and states that this lesion occurs more frequently in the sixth and seventh than in other decades of life. The youngest patient noted in a review of the literature was 22 years of age and the oldest 89 years of age. Of the patients whose sex was stated, 33.7 per cent were women and 66.3 per cent were men.

The right ureter was involved in 67 per cent of the cases, and the lower end of the ureter in 52 per cent.

More than 50 per cent of the tumors were papillary.

The postoperative mortality rate was 24 per cent. Only 6 patients were reported living and well more than four years after operation, but many of the patients were not followed. Of 32 reported well, only 6 were followed four years or more.

Earlier diagnosis and use of operative procedures that have as their first consideration the removal of the primary lesion with the least possible risk to the patient should decrease the postoperative mortality rate and improve the end results.

²¹ Scott, W. W. A Review of Primary Carcinoma of the Ureter. Presenting Two Cases, J Urol 50 45-64 (July) 1943.

Injury During Gynecologic Operations—Adams²² discusses ureteral injury incurred during gynecologic operations, presenting data on a series of 73 cases collected from the literature between 1936 and 1941, he also reports 3 new cases. No information as to the frequency of this accident is available from his study. Sampson has reported 16 cases of ureteral injury occurring at the Johns Hopkins Hospital between 1889 and 1902 in 4,086 major gynecologic procedures, an incidence of 0.4 per cent. Likewise Newell in 1939 found an occurrence of 0.4 per cent in 3,144 hysterectomies. Ureteral injury can pass unrecognized, Newell reported 15 cases, in 6 of which the injuries were not recognized until found at necropsy.

In the present series the injuries were unilateral in 50 cases and bilateral in 17. There are five general types of injuries: (1) ligation, (2) incision, (3) excision, (4) necrosis and (5) obstruction from surrounding postoperative edema and inflammation.

The most concise tabulation of the sequelae of ureteral damage in cases in which this condition has not been discovered at the time of operation has been formulated by Robinson and is quoted by Adams: (a) Bilateral damage: (1) double section followed by leakage, general infection and death (or formation of a fistula), (2) double ligation followed by anuria and uremia, fatal if unrelieved. (b) Unilateral damage: (1) section followed by leakage and acute infection either local or widespread, (2) partial section with leakage and ureteroabdominal or ureterovaginal fistula, (3) ligation followed by atrophy of the kidney, with or without symptoms of renal inadequacy, and in some cases by acute or chronic uremia, (4) ligation with reflex suppression and complete anuria. (c) Partial occlusion or kinking from periureteral adhesions following various abdominopelvic operations. Adams adds the following two classifications: (d) Unilateral or bilateral ligation with delayed formation of a fistula. (e) Unilateral or bilateral occlusion from edema and inflammation with spontaneous reestablishment of renal drainage.

The treatment of the ureteral injury depends on when the condition is recognized and what type of damage has occurred. When the injury is recognized during the course of an operation, immediate restoration of the continuity of the kidney and the bladder should be attempted. In the present series the condition was recognized only eight times, compared with sixty-

seven times that the accident was not discovered until the postoperative period.

When the ureter has been severed, the two procedures of choice are ureteroureteral or ureterovesical anastomosis.

Voluntary ligation of the proximal end of the ureter should be done only when the patient is in such poor condition that further operative procedure will seriously endanger her life.

When clamping or ligation of the ureter is recognized at the time of operation, the clamp or the ligature should be removed immediately. However, a clamp or a ligature, even though left on for only a short time, often will jeopardize the integrity of the ureteral wall. When any doubt of ureteral integrity exists, it is better to excise the damaged portion and to do a ureteroureteral or ureterovesical anastomosis.

In 2 of the 8 cases in which damage was recognized at the time of operation it was treated by ureterovesical anastomosis, with a good result in 1 and ureteral stricture and renal atrophy in 1. In another case the damage was corrected by implanting the ureter into the bowel, with a good result. In 5 cases ureteroureteral anastomosis was attempted, good results were obtained in 3, in 1 instance in which this operation failed to give a good result the function was good after dilation of the ureter but the unavoidable discontinuance of dilation resulted in ureteral stricture. There was 1 death.

A study of the data on cases collected by Adams together with a series collected by Femers yields several interesting facts.

Ureterovesical anastomosis was done in 70 cases. In 8 (11.4 per cent) the result was considered to be perfect, a fair result (some residual stenosis) was observed in 38 (54.3 per cent). In 21 (30 per cent) the result was a failure and in 3 (4.3 per cent) the operation was followed by death of the patient.

In 30 cases ureteroureteral anastomosis was performed. In 21 (70 per cent) it yielded a successful result, in 6 (20 per cent), a failure, in 3 (10 per cent) death followed the operation.

In 23 cases in which the ureter was ligated intentionally there were two deaths, while in 53 cases of nephrectomy there were only two deaths, an incidence of 3.8 per cent. It would seem, therefore, that when the kidney is to be sacrificed, nephrectomy is the better of the two procedures.

There were 25 cases in which the fistula was reported to have healed spontaneously. However, in 10 of these subsequent study showed the kidney on the affected side to have been destroyed. Spontaneous closure of a fistula in

²² Adams, T. W. Ureteral Injury During Gynecologic Surgery, *West J Surg* 51:305-320 (Aug) 1943.

these cases, therefore, should not be looked on with a great feeling of security

Of the 255 cases in which secondary procedures were carried out, death or removal of one kidney occurred ninety-four times

Bilateral ureteral occlusion cannot go long unrecognized. The symptoms are anuria and gradually developing uremia. Failure to obtain urine from the bladder in twelve hours following a pelvic operation calls for immediate investigation. Should this investigation prove bilateral ureteral occlusion, immediate steps must be taken to establish urinary drainage. In the present series, anuria was the first symptom noted in 16 of the 17 cases. The length of time that the anuria was allowed to proceed before relief measures were undertaken was from twelve hours to six days.

In these cases the primary object is the immediate relief of the anuria. There are in general two methods of attack: (1) reestablishment of drainage of the ureteral tract, (2) temporary replacement of drainage above the point of injury by either unilateral or bilateral nephrostomy or ureterostomy.

Spasm—Lund and Zingale²³ discuss a synthetic hydrocarbon (methylaminoisooctene) for the relief of ureteral spasm, reporting a series of 100 consecutive cases in which the drug was used.

In 80 cases there was obtained a varying degree of relief. In 50 per cent of these relief was complete. In 30 per cent there was relief sufficient to cause the patient to feel comfortable. In the remainder of the cases, 20 per cent, there was no relief. In this last class are included patients that were having postcystoscopic colic; it was assumed that the causative factor, the radiopaque solution, had not been drained off completely and remained as an irritant. In this class also are those patients in whom a demonstrable foreign body was present.

In 8 cases, Lund and Zingale believe, the drug was instrumental in causing spontaneous passage of stones that were present.

There were 2 patients with sensitivity to the drug. This sensitivity was manifested by a feeling of light-headedness and increased nervous irritability, and 1 of these experienced difficulty in swallowing. These effects were transient and occurred among unusually apprehensive women.

There was no cumulative effect or habituation.

This synthesized aliphatic hydrocarbon is a sympathomimetic drug and probably acts on the true sympathetic endings which are inhibitory

to the ureters. With the dosage used, side effects have been negligible. The drug has been effective in ureteral colic due to stone, postcystoscopic colic, ureteral spasm following pyelography and ureteral hyperirritability on a neurogenic basis; it has assisted the passage of stones. In Lund and Zingale's opinion it is a most effective ureteral antispasmodic.

Injury by Radium—Smith and Leadbetter²⁴ report 5 cases of ureteral obstruction following radium treatment of the cervix or the vagina. In 2 of these, microscopic examination of the ureter and of the adjacent vesical wall did not show any cancer cells; in 1 instance the complete restoration of the ureteral lumen following nephrostomy may be accepted as proof that the obstruction was not directly due to cancer. From the evidence at hand it appears that obstruction is caused much more frequently by radium than by roentgen therapy. If the obstruction involves the intramural portion of the ureter and appears to be due to late radiation effect rather than to infiltration by cancer cells, temporary diversion of the urine by means of nephrostomy is indicated. If the obstruction develops at a higher point, permanent urinary diversion by nephrostomy or by ureterostomy usually will be necessary.

BLADDER

Calculus—Nation²⁵ reports a case of large vesical calculus in association with gigantism. The patient, a 33 year old man, had had symptoms for only a short period. He was 6 feet 4½ inches (194 cm) tall, with characteristics suggestive of gigantism. A roentgenogram of the bladder revealed a shadow 8 by 10 cm in the region of the bladder and a somewhat smaller one below this. Cystolithotomy was carried out and the stones removed. The patient made an immediate operative recovery but died twenty days later.

Abramson^{26a} discusses the solution of vesical phosphatic calculi. He reports a case demon-

²⁴ Smith, G. G., and Leadbetter, W. F. The Effect of Irradiation on the Lower Ureters, *Tr. Am. A. Genito-Urin. Surgeons* (1942) **35** 195-203, 1943.

²⁵ Nation, E. F. Large Vesical Calculus in Association with Gigantism, *California & West Med* **59** 167-169 (Sept.) 1943.

²⁶ (a) Abramson, D. J. Solution of Vesical Phosphatic Calculi, *J. Urol.* **50** 197-201 (Aug.) 1943. (b) Suby, H. I., Suby, R. M., and Albright, F. Properties of Organic Acid Solutions Which Determine Their Irritability to the Bladder Mucous Membrane and the Effect of Magnesium Ions in Overcoming This Irritability, *ibid.* **48** 549-559, 1942. (c) Suby, H. I., and Albright, F. Dissolution of Phosphatic Urinary Calculi by the Retrograde Introduction of a Citrate Solution Containing Magnesium, *New England J. Med.* **228** 81-91 (Jan. 21) 1943.

²³ Lund, H. G., and Zingale, F. G. Synthetic hydrocarbon for the Relief of Ureteral Spasm, *J.* **50** 65-67 (July) 1943.

strating the efficacy of citric acid-magnesium oxido-sodium carbonate solution ("solution G" [Suby, Suby and Albright^{26b}, Suby and Albright^{26c}]) in dissolving a vesical calculus when surgical intervention was contraindicated. The patient was a man aged 64 years, who had nocturia, dysuria and urgency. Cystoscopic examination revealed an enlarged prostate. Suprapubic cystotomy was done and later transurethral resection. The patient responded poorly to surgical treatment. In due time the suprapubic sinus closed. At a later date the patient had symptoms suggesting a vesical calculus. A roentgenogram showed a shadow 2 by 3 cm in the region of the bladder. Because of his advanced age and the poor condition of his heart, an attempt was made to dissolve the stone with the citric acid solution. Irrigations were started and continued for six days. The washings contained a great deal of sediment. On cystoscopy the calculus was found to be considerably reduced in size. Later cystoscopy revealed that the calculus had disappeared.

Abramson also discusses the prophylaxis of vesical phosphatic calculi. Stasis from whatever cause must be corrected. Sulfonamide compounds have proved of some value in combating infections caused by *Bacillus coli*, *Bacillus proteus* or staphylococci. Other drugs include mandelic acid, methenamine and ammonium chloride. The acid ash regimen may be prescribed to render the urine acid and thus prevent precipitation of phosphates. The urine should be maintained approximately at pH 5.0. In the presence of a persistent alkaline infection, however, the pH of the urine cannot usually be changed to the acid side. Fluids, preferably distilled water, should be forced. The more dilute the urine, the less chance there is of precipitation occurring. Vitamin A in large doses is indicated. Lavage with antiseptic and dilute acid solutions is of value. The citric acid solution is also effective in the treatment of alkaline incusted cystitis.

Carcinoma—Priestley and Strom²⁷ state that until recent years total cystectomy for carcinoma of the bladder usually had been employed only for the far advanced and so-called desperate type. Only for this type could the surgeon justify a procedure which was attended by so high an operative mortality rate. Total cystectomy has been employed for the most part in cases in which many forms of treatment had been tried previously and in which all other measures had

proved to be futile. Obviously this means that the growth is of long standing.

In these cases, regarding a second objection, namely, the high immediate postoperative mortality rate, it has been observed that the bladder can be removed completely with a reasonable mortality rate provided proper attention is paid to preoperative and postoperative care as well as to the actual surgical technique. If the operative mortality rate of bilateral ureterosigmoidostomy and total cystectomy can be kept within a reasonable limit, the application of this method of treatment for vesical neoplasm should become broader than it is at present, provided of course, one admits that there are certain types of cases for which the operation gives the best chance of cure.

Indications for total cystectomy in the treatment of carcinoma of the bladder are far from standardized. This is true largely because there is lacking experience with a large series of cases in which operation has been performed a number of years previously, so that ultimate survival rates could be ascertained in relation to the types of lesion present. During the last few years Priestley and Strom have employed total cystectomy in four main groups of cases with the hope of determining as time passes whether these indications are correct. These groups of cases include (1) cases in which there is great extension of a low grade neoplasm, (2) cases in which there is repeated recurrence of a low grade neoplasm, (3) cases in which there are multiple foci of origin of the neoplasm and (4) cases in which there is a high grade neoplasm which remains confined to the bladder so far as the best available information, obtained by both clinical investigation and exploratory operation, shows.

The best ultimate results following total cystectomy probably will be observed in the first three groups of cases, as the high grade lesion is likely to recur in one form or another despite any type of treatment.

There is also another group of cases in which total cystectomy may be employed. These are the cases in which the neoplasm is sessile and involves the trigone and the base of the bladder. Often under these circumstances some disposition must be made of the ureters if the lesion is to be removed completely by any form of therapy.

The most satisfactory plan of procedure, in Priestley and Strom's opinion, is simultaneous bilateral ureterosigmoidostomy followed after an interval of two or three weeks by total cystectomy combined with removal of the prostate gland and the seminal vesicles. One may trans-

²⁷ Priestley, J. T., and Strom, G. W. Total Cystectomy for Carcinoma of the Bladder, *J. Urol.* **50**: 210-227 (Aug.) 1943.

plant each ureter to the bowel at a separate stage and remove the bladder at a third operation

One of the factors which are most important in obtaining satisfactory results following ureterosigmoidostomy is proper preoperative preparation of the patient. Priestley and Strom carry out a program similar to that employed before resection of the large bowel for carcinoma. This includes a regimen of preparation extending over a minimum of four days. During this interval the patient should receive a residue-free liquid diet with supplements of hard candy and vitamins. During the first three days of preparation a saline laxative is given in the morning and again in the evening. One of the sulfonamide drugs which is effective in reducing the bacterial content of the gastrointestinal tract should be administered in adequate doses every two hours during the four days of preparation. During the first several days an enema of generous size is given each morning and each evening. During the last two days of preparation the rectum is irrigated with warm saline solution twice a day until the returns are clear. On the night prior to operation the saline laxative and the rectal irrigation are omitted and 2 fluidrachms (7.4 cc.) of camphorated tincture of opium U. S. P. is administered at 6 and at 10 p. m., and aspiration of the rectum is conducted for thirty minutes at the same time. On the day of operation 2 fluidrachms (7.4 cc.) of camphorated tincture of opium U. S. P. is given and rectal aspiration is conducted for thirty minutes at 6 and at 8 a. m.

Simultaneous bilateral ureterosigmoidostomy is then performed.

Following bilateral ureterosigmoidostomy, the rectal tube is kept in place for a week or ten days. During this interval care must be taken that the tube does not become plugged. Removal of the bladder is postponed until the patient has recovered his strength fairly well and is able to be out of bed for a few days. This usually means an interval of approximately three weeks between the two operations.

Spinal anesthesia, often combined with intravenous administration of pentothal sodium, is used for removal of the bladder. The patient is placed in the Trendelenburg position, and the bladder is exposed extraperitoneally through a low midline incision. If there is no extension of the malignant process into the perivesical tissues, the bladder can be mobilized by blunt dissection for the most part. Sharp dissection is employed where necessary. Generally it is preferable to mobilize first the side of the bladder in which the neoplasm is not present by pushing the peritoneum back and dissecting away the

perivesical tissues down toward the base of the bladder.

By blunt dissection the seminal vesicles and the prostate are separated from the rectum and mobilized with the bladder. The bladder then is freed upward anteriorly, and after complete mobilization, is held attached only by the urethra. This is severed distal to the verumontanum. It is preferable for several reasons to remove the prostate and the seminal vesicles along with the bladder. If these are not removed, recurrence of the vesical neoplasm may take place in the prostatic urethra, as occurred in 2 of the earlier cases in the experience of Priestley and Strom. Occasionally, if the growth in the bladder is situated in the region of the trigone, it may have penetrated into the prostate, a condition which would make removal of the latter desirable. In addition, one may find an entirely independent and unsuspected neoplasm of the prostate. Removal of the bladder, seminal vesicles and prostate together can be accomplished more readily than removal of the bladder alone. If one removes only the bladder and leaves the prostate and the seminal vesicles intact, dissection around the base of the bladder is more difficult and lines of cleavage are less satisfactory than if the prostate and the seminal vesicles are removed with the bladder. Total cystectomy is easier in women than in men and does not present any special problems when a woman is the subject.

Priestley and Strom recently made a review of the records of 105 patients with carcinoma of the bladder on whom operation was performed at the Mayo Clinic between 1910 and Aug. 31, 1942, inclusive, with a view to performing total cystectomy. The operations were performed by seven different surgeons. In approximately 1 of every 5 patients the growth was considered to be inoperable, and exploration and biopsy alone were done. In a group of 71 patients in whom urinary diversion was accomplished by various methods as a preliminary step to cystectomy, the operative mortality rate (hospital deaths) was 23.9 per cent. Of this group of 71, bilateral ureterosigmoidostomy was performed in 51, with a mortality rate of 15.7 per cent. In the remaining 20 patients, many of whom were in unusually poor condition, urinary diversion was accomplished by other methods, with a mortality rate of 45.0 per cent. In 4 of the entire group of 71 patients ureteral transplantation was performed as a palliative procedure, and 2 of these patients failed to survive the operation. Of the patients who survived transplantation, cystectomy was performed in 52, with six deaths, or a

mortality rate of 11.5 per cent. In addition, transplantation and total cystectomy were performed in one stage in 13 patients, with eight deaths, or a mortality rate of 61.5 per cent.

It is of interest to review in contrast with these figures the experience of the past three years. During this interval ureteral transplantation has been performed in 29 patients, with one death. Simultaneous bilateral uterosigmoidostomy was the method of transplantation employed in 27 of these 29 patients. Of the 28 patients who survived ureteral transplantation and in whom cystectomy was accomplished, 1 died. Thus the operative mortality rate in 29 patients for both operations was 6.9 per cent. In 5 additional patients ureteral transplantation and cystectomy were performed in one stage, with one death.

In all there were 51 patients who survived total cystectomy for carcinoma of the bladder. Of this group, 26 have succumbed since operation, and 15 of these died within the first post-operative year, the remainder died at intervals ranging from one to six and a fourth years after operation. The cause of death was ascertained for 20 of the group of 26 patients. Metastasis was the cause in 16, in 4 death resulted from renal failure. A review of the records of the patients who died of metastasis reveals a fact which appears significant. In 13 of this group extension of carcinoma beyond the bladder either to the perivesical tissues or to the regional lymph nodes was noted at the time of operation. Because of this fact it appears unwise to perform cystectomy if the growth has extended beyond the bladder in such a manner that its complete removal is questionable. Of the group of 51 patients who survived cystectomy, 24 are still alive and 1 could not be traced.

Abeshouse and Goldstein²⁸ review 89 reported cases of primary malignant neoplasm in a diverticulum and add data on 4 personal cases.

They state that primary neoplasm in a diverticulum is essentially a disease of men and occurs most frequently between the ages of 50 and 65 years. The growth may be benign or malignant and closely simulates that originating in the bladder. The most common tumor observed is a carcinoma of epithelial origin, either squamous cell or papillary carcinoma. The most common and most important symptom is hematuria. Other symptoms frequently noted are those associated with infection of the bladder and the diverticulum or obstruction of the vesical neck.

Cystoscopy and cystography are important diagnostic aids. The diagnosis is made easily in cases in which a portion of the tumor protrudes through the orifice of the diverticulum and can be seen through the cystoscope or in which the tumor can be visualized directly when the cystoscope is introduced into the diverticulum. In the diverticulogram bleeding from the orifice of the diverticulum and filling defects are strongly indicative of a tumor.

Every diverticulum observed at operation, regardless of its cause, should be exposed and inspected carefully, and if suggestive of cancerous growth, it should be removed. The diverticulum containing the neoplasm may be also the seat of infection or of a stone. Lesions of the urinary tract are frequent complications of this condition.

Surgical treatment has been far from satisfactory but yields better results from the standpoint of symptomatic relief and cure than nonoperative treatment. The operation of choice is excision of the diverticulum and tumor by the suprapubic intra-vesical or extra-vesical method or a combination of the two. Patients who have extensive local or general metastatic growths or severe infection of the urinary tract and those who are poor surgical risks should not be subjected to radical operative treatment. The prognosis is bad, as relatively few cures are reported, and the majority of patients succumb within two years after operation.

Rupture—McCague²⁹ discusses the factors influencing mortality and morbidity in patients with intrapelvic rupture of the urethra and bladder. The incidence of urethral injury due to external violence is not high. The incidence of traumatic rupture of the urethra and bladder that occurs as a complication of fracture of the bony pelvis is somewhat higher in the Pittsburgh district than in any other area recorded in the literature—this by reason of the large numbers of men employed in the heavy industries, especially the coal mines and the steel mills. Fifty-two cases of pelvic fracture were encountered by McCague from January 1940 to May 1942. Five patients suffering from rupture of the urethra and bladder complicating pelvic fracture have been admitted to McCague's service since Pearl Harbor. All the injuries except 1 were due to industrial accidents. Such an injury sustained in a coal mine is usually the result of the patient's being crushed between the mine

28 Abeshouse, B. S., and Goldstein, A. E. Primary Carcinoma in a Diverticulum of the Bladder. A Report of Four Cases and a Review of the Literature, *J. Urol.* 49: 534-557 (April) 1943.

29 McCague, E. J. Factors Influencing Mortality and Morbidity in the Intrapelvic Ruptures of Urethra and Bladder, *Tr. Am. A. Genito-Urin. Surgeons* (1942) 35: 307-316, 1943.

timbers and a coal car or of his being buried beneath a fall of slate. The damage is violent and mutilating, usually there are multiple fractures of the pelvis, intrapelvic rupture of the urethra and bladder, frequently associated visceral injuries and shock so profound that many of the patients die (23 per cent) before or in spite of all remedial measures.

Diagnosis may be difficult. With rare exceptions the patient is admitted in profound shock, there are extreme pain on movement and inability to move the legs, which generally are rotated outward. The patient is unable to void, and blood may be seen trickling from the meatus. Palpation of the iliac crests and compression of the pelvis cause great pain, and crepitus usually can be elicited. The urethra generally is severed and displaced posteriorly, the rectum is compressed and a tender boggy mass may be felt and bony deformity outlined. Perineal and scrotal ecchymosis or hematoma may be present. Unless there is an associated rupture of the bladder, these patients do not extravasate urine early, owing to the reflex action of the sphincter.

If there is an associated rupture of the bladder, there is marked tenderness in the lower part of the abdomen, usually over the site of the rupture and the rapidly developing hematoma produces a palpable tender mass, enlarging and distorting the lower part of the abdomen. There is nearly always traumatic ileus, which makes the diagnosis of intraperitoneal rupture of the bladder or visceral injury difficult. As a rule, however, intraperitoneal injuries are more dramatic than extraperitoneal injuries, there are greater shock, a rigid boardlike abdomen, absence of peristalsis and great tenderness, whereas in extraperitoneal rupture of the bladder tenderness is more marked in the lower part of the abdomen. In McCague's opinion, the passing of a catheter in these cases is rarely indicated, and the information gained is misleading and unreliable.

In McCague's opinion, refinements of diagnosis are rarely necessary for intrapelvic rupture of the urethra and bladder. They have little or no influence on the management, and the unnecessary movement and manipulation of a badly fractured pelvic girdle may increase the gravity of the condition. The delay necessary and the emotional trauma may be factors in mortality. Documentation of any sort is definitely contraindicated in these cases.

The major cause of death in the patients with intrapelvic injuries who survive the primary injury is urinary extravasation and sepsis. Among those that have an intraperitoneal complication, i. e., intraperitoneal rupture of the

bladder and associated visceral damage, the cause is mainly extravasation and peritonitis.

The main causes of morbidity are failure of early preservation of the continuity of the urethra, causing long-standing complications difficult to correct, formation of calculi with grave damage to the urinary tract unless prevented, loss of sexual power, due to injury of the nerve supply or of the cavernous bodies, and early infection of the soft parts of the pelvic cage with secondary involvement of the bony structures.

McCague stresses the importance of immediate preservation of the continuity of the urethra. Failure to do so results in serious complications. There is a large gap between the torn ends of the urethra. This space is filled with fibrous tissue, making extensive secondary operations for the correction of the defect necessary—procedures that are difficult and not always satisfactory in accomplishment.

McCague has not resorted to sutures and anastomosis in these cases; it is not necessary and lengthens the operation. The retrograde splinting of the entire urethra with the legs in extension has been sufficient for approximation and epithelialization.

Formation of calculi is fairly common in this group by reason of the marked increase of urinary excretion of calcium, the stasis and the infection as well as the prolonged rest in bed. Measures to prevent this complication are maintenance of the urinary pH on the acid side, high acid ash diet, acidifying medication, frequent elevation of renal level and administration of large quantities of fluids.

In McCague's clinic the formation of stricture has been encountered more frequently in the straddle injuries than in intrapelvic ruptures. Periodic dilation is necessary.

Impotence occurs as a complication in a small number of these cases, owing to injury of the nerve and blood supply or of the cavernous bodies.

Diverticula—Llanos³⁰ states that the majority of the diverticula of the bladder are congenital but that some are produced by obstruction to urination of long standing or are, at least, small congenital diverticula that did not exhibit any symptoms until they were enlarged because of urinary obstruction, the pedicles becoming narrowed and elongated, resulting in conditions that produce more or less accentuated disturbances.

The seriousness of the diverticula depends in large measure on their location. Those of the posterior wall—immediately behind the trigone—

30 Llanos, M. A. Diverticula of the Bladder, *J Urol* 49:628-638 (May) 1943.

a pathognomonic appearance in the original films. The shining light reflected from the individual gas-containing cysts on cystoscopy is so characteristic as to be unmistakable for any other condition. The transient nature of the condition probably accounts for its rare description.

Vesicovaginal Fistula — Valme³⁴ discusses transvesical (suprapubic) closure of a vesicovaginal fistula. The bladder should be opened suprapubically, disclosing the fistula, which is usually a little above the vesical neck. In one of the cases in which Valme operated, the fistula was parallel to a line drawn from the vesical neck to the orifice of the right ureter. The orifice of the left ureter was retracted. He resected the fistula and repaired the vesicovaginal fistula, suturing the vesical and vaginal walls separately. Ureteral catheters were placed in the ureters. Twelve days after this operation the patient voided normally without a drop of vaginal leakage. The anterior vaginal wall regained its elasticity and did not present any cicatricial zone.

The operation usually comprises the following steps: (1) suprapubic exposure of the bladder, (2) suprapubic cystotomy and introduction of vesical retractors, (3) resection of the fistula, (4) repair of the vaginal wall, (5) closure of the vesical wall, (6) ureteral catheterization and closure of the bladder. A sterile glass tube is introduced into the vagina up to the cervix, so as to obtain a solid base and also to fix the trigonal area. After the bladder has been opened, and the retractors have been introduced, the fistulous tract is carefully excised. The excision is followed by the separation of the bladder and vaginal walls, which are sutured separately. The ureters then are catheterized with catheters the ends of which have been cut and which are inserted to a distance of 12 cm. above the ureteral orifices. The catheters then are removed, and the bladder is closed.

Neural Lesions — Smith and Strasberg³⁵ investigated 50 cases of neurogenic and cord bladder. Contrary to the common belief in urologic literature that dilatation of the ureter and renal pelvis accompanies neurogenic and cord bladder, they did not encounter a single case of dilatation of the ureter and renal pelvis. Tests of renal function applied to the group did not demonstrate any impairment of function. Forty-four of the group were patients suffering from

syphilis (Wassermann reaction of the spinal fluid positive), the remaining 6 included patients who had transection or tumor of the spinal cord, tumor of the frontal lobe, epilepsy, cerebral arteritis or subarachnoid hemorrhage. Smith and Strasberg define a disturbance of the bladder as neurogenic when in the absence of any urethral obstruction the line on the graph definitely deviates from the normal, either toward a horizontal position, (an atonic bladder) or toward a vertical direction (a hypertonic bladder). A cystometrographic study was made on each patient. In the series 3 had hypertonic and the remainder either hypotonic or atonic bladders. The syphilitic patients were in the last classification, and this was subdivided further into those with early, preclinical hypotonic bladders and those with inert, atonic bladders and long-standing urinary retention, as evidenced by a flat curve. In approximately 50 per cent the residual urine amounted to from 30 cc. to almost the entire amount collected.

PROSTATE

Carcinoma — Colston³⁶ made a study of the radical operations for carcinoma of the prostate performed in the Brady Urological Institute during a five year period, to determine the percentage of cases suitable for radical operation out of all cases of carcinoma of the prostate encountered in the institute.

There were 4 who died in the hospital in the series of 73 patients operated on—a mortality rate of 5.5 per cent. Of 43 patients for whom the prognosis was good, 41 are living and well without evidence of recurrence or metastasis. Of 26 patients for whom the prognosis was poor, 8 are living and well from three months to five years after operation.

Intensive follow-up of all patients who had early cancer of the prostate and on whom Young's radical operation was performed showed that more than 50 per cent were free from recurrence or metastasis from five to twenty-seven years after leaving the hospital. A study of the postoperative functional results was also carried out on the 69 patients who comprise this series. In 49 the functional result was excellent, all having complete urinary control. The result was classified as fair in 11, who noted occasional slight leakage during the day, and in 8 the result was evaluated as poor, since some form of apparatus was neces-

34 Valme, W. Transvesical (Suprapubic) Closure of Vesicovaginal Fistula, *J Urol* 50:40-41 (July) 1943.

35 Smith, E., and Strasberg, A. The Upper Urinary Tract in Cases of Neurogenic Bladder. Preliminary Communication, *J Urol* 49:803-807 (June) 1943.

36 Colston, J. A. C. Carcinoma of the Prostate. A Study of the Percentage of Cases Suitable for the Radical Operation, *J A M A* 122:781-784 (July 17) 1943.

a pathognomonic appearance in the original films. The shining light reflected from the individual gas-containing cysts on cystoscopy is so characteristic as to be unmistakable for any other condition. The transient nature of the condition probably accounts for its rare description.

Vesicovaginal Fistula—Valme³¹ discusses transvesical (suprapubic) closure of a vesicovaginal fistula. The bladder should be opened suprapubically, disclosing the fistula, which is usually a little above the vesical neck. In one of the cases in which Valme operated, the fistula was parallel to a line drawn from the vesical neck to the orifice of the right ureter. The orifice of the left ureter was retracted. He resected the fistula and repaired the vesicovaginal fistula, suturing the vesical and vaginal walls separately. Ureteral catheters were placed in the ureters. Twelve days after this operation the patient voided normally without a drop of vaginal leakage. The anterior vaginal wall regained its elasticity and did not present any cicatricial zone.

The operation usually comprises the following steps: (1) suprapubic exposure of the bladder, (2) suprapubic cystotomy and introduction of vesical retractors, (3) resection of the fistula, (4) repair of the vaginal wall, (5) closure of the vesical wall, (6) ureteral catheterization and closure of the bladder. A sterile glass tube is introduced into the vagina up to the cervix, so as to obtain a solid base and also to fix the trigonal area. After the bladder has been opened, and the retractors have been introduced, the fistulous tract is carefully excised. The excision is followed by the separation of the bladder and vaginal walls, which are sutured separately. The ureters then are catheterized with catheters the ends of which have been cut and which are inserted to a distance of 12 cm. above the ureteral orifices. The catheters then are removed, and the bladder is closed.

Neural Lesions—Smith and Strasberg³² investigated 50 cases of neurogenic and cord bladder. Contrary to the common belief in urologic literature that dilatation of the ureter and renal pelvis accompanies neurogenic and cord bladder, they did not encounter a single case of dilatation of the ureter and renal pelvis. Tests of renal function applied to the group did not demonstrate any impairment of function. Forty-four of the group were patients suffering from

syphilis (Wassermann reaction of the spinal fluid positive), the remaining 6 included patients who had transection or tumor of the spinal cord, tumor of the frontal lobe, epilepsy, cerebral arteritis or subarachnoid hemorrhage. Smith and Strasberg define a disturbance of the bladder as neurotic when in the absence of any urethral obstruction the line on the graph defined deviates from the normal, either toward a horizontal position (an atonic bladder) or toward a vertical direction (a hypertonic bladder). A cystometrographic study was made on each patient. In the series 3 had hypertonic and the remainder either hypotonic or atonic bladders. The syphilitic patients were in the last classification and this was subdivided further into those with early, preclinical hypotonic bladders and those with more atonic bladders and long-standing urinary retention as evidenced by a flat curve. In approximately 50 per cent the residual urine amounted to from 30 cc. to almost the entire amount collected.

HOPEFUL

Carcinoma—Colston³³ made a study of the radical operations for carcinoma of the prostate performed in the Brady Urological Institute during a five year period, to determine the percentage of cases suitable for radical operation out of all cases of carcinoma of the prostate encountered in the institute.

There were 4 who died in the hospital in the series of 73 patients operated on—a mortality rate of 5.5 per cent. Of 43 patients for whom the prognosis was good, 41 are living and well without evidence of recurrence or metastasis. Of 26 patients for whom the prognosis was poor, 8 are living and well from three months to five years after operation.

Intensive follow-up of all patients who had early cancer of the prostate and on whom Young's radical operation was performed showed that more than 50 per cent were free from recurrence or metastasis from five to twenty-seven years after leaving the hospital. A study of the postoperative functional results was also carried out on the 69 patients who comprise this series. In 49 the functional result was excellent, all having complete urinary control. The result was classified as fair in 11, who noted occasional slight leakage during the day, and in 8 the result was evaluated as poor, since some form of apparatus was neces-

34 Valme, W. Transvesical (Suprapubic) Closure of Vesicovaginal Fistula, *J Urol* 50:40-41 (July) 1943.

35 Smith, E., and Strasberg, A. The Upper Urinary Tract in Cases of Neurogenic Bladder. Preliminary Communication, *J Urol* 49:803-807 (June) 1943.

36 Colston, J. A. C. Carcinoma of the Prostate. A Study of the Percentage of Cases Suitable for the Radical Operation, *J A M A* 122:781-784 (July 17) 1943.

sary during the day and in some instances during the night

Herbst³⁷ discusses histopathologic studies of prostatic carcinoma under endocrine treatment. He concludes that from the microscopic standpoint no changes occur that are characteristic of any modification of carcinoma of the prostate cells as observed with present methods of staining. This study suggests the necessity for further interest and experimentation with certain biochemical staining methods in an attempt to bring out changes, if they exist, so that they can be recognized.

Quinland³⁸ presents a study of 34 cases of cancer of the prostate in Negroes. The patients ranged in age from 42 to 106 years. The average age of the patients on whom operation was performed was 60 years, while the age of those on whom necropsy was performed averaged 70 years. One patient on whom prostatectomy was done for cancer underwent nephrectomy for nephrolithiasis three years and four months later and is alive and working four years and eight months after the prostatectomy. Cancerous growths ranging from microscopic inclusions to a huge mass of 720 Gm were studied with the disclosure that extensive and generalized metastatic growths were more frequent with the scirrhous type of carcinoma than with other types. The 18 per cent incidence in this collection is comparable to percentages reported from other clinics.

Henline,³⁹ in discussing carcinoma of the prostate, states that there are three general regions within the prostate which may be involved in a pathologic process and three main types of prostatic disease. It is usual for each type of pathologic change, at least during its inception, to limit itself to a particular region, but any combination of these distinct entities may coexist.

The two lateral lobes, usually referred to as the functioning prostatic glands, are the seat of prostatic infections. Bacteria may invade the deep recesses of these tortuous glands in the lateral lobes and produce acute or chronic prostatitis or a prostatic abscess, or the lobes may be the seat of endogenous prostatic calculi. According to recent investigations, the function-

ing portions of these lateral lobes are rarely the site of origin of either prostatic hyperplasia or cancer.

Hyperplasia of the prostate develops just beneath the urethra. Denning and Wolf in a recent study of 210 prostates showed that hyperplasia is seen first as a fibromuscular mass in the muscular wall of the prostatic urethra, which lies close to the urethra.

Carcinoma develops as a distinct pathologic process in the prostate and is not related to either infection or hyperplasia of the prostate. Carcinoma usually develops in the posterior lobe a region rarely, if ever, affected by either infection or hyperplasia.

Carcinoma of the prostate develops in approximately 15 per cent of men past 50 years of age. The incidence increases with advancing years. When it is considered that 1 in every 7 men past 50 years of age has carcinoma of the prostate, the importance of this lesion in advancing years becomes apparent. It also becomes obvious that many prostatic cancers must progress slowly, otherwise extensive carcinomatosis and death from prostatic carcinoma would be an even more frequent finding among elderly men than it is.

The most common site of origin of carcinoma of the prostate is the posterior lobe. This lobe is the portion of the gland posterior and posterolateral to the fan-shaped ducts which enter the sides of the urethra. The function of this lobe, if any, is unknown, and it remains dormant from birth until some changes occur.

Detection of the presence of early carcinoma of the prostate devolves on the physician who examines patients periodically for their general health. Carcinoma may be confused with fibrosis. The age of the patient may tend to relieve one's suspicion of a malignant lesion. Fibrosis frequently is somewhat less hard than a malignant lesion. One may also confuse an early malignant lesion with prostatic calculi. The latter may be located so near the capsule that differentiation by palpation is impossible. Roentgenologic examination will aid in making the diagnosis of calculi.

When a suggestive nodule is palpated in the prostate, Henline advises a perineal exposure in order to take a specimen of the nodule for biopsy.

Henline states that "complete prostatectomy" refers to the removal of the entire prostate with its capsule and the entire prostatic urethra. Such complete removal is necessary to eradicate the disease and can be done only by the perineal approach. The line of cleavage which permits hyperplastic prostatic tissue to be enucleated

37 Herbst, W. P. Histopathologic Studies in Prostatic Carcinoma Under Treatment by Castration, the Injection of Diethylstilbestrol or Both, *Tr. Am. A. Genito-Urin. Surgeons* (1942) **35** 337-343, 1942.

38 Quinland, W. S. Cancer of the Prostate. A Clinicopathologic Study of Thirty-Four Cases in Negroes, *J. Urol.* **50** 228-236 (Aug.) 1943.

39 Henline, R. B. The Diagnosis and Treatment of Early Carcinoma of the Prostate, *J. A. M. A.* **122** 785-789 (July 17) 1943.

suprapubically leaves behind the entire posterior lamella from which most cancerous growths arise. Transurethral resection also removes the hyperplastic tissue but the so-called capsule, which is the posterior lamella of tissue, is of necessity left behind. Thus, if carcinoma is not found in the tissue removed either by suprapubic prostatectomy or by transurethral resection, there still is no assurance that carcinoma of the prostate is not present. Henline has had several patients who sought relief after each of these operations because of carcinoma of the prostate in the portion of the gland left behind.

Sarcoma—Melicow, Pelton and Fish⁴⁰ reported 4 cases of sarcoma of the prostate. 2 of fibrosarcoma, the patients being aged 34 and 18 years, 1 of rhabdomyosarcoma, the patient being aged 16 years, and 1 of reticulum cell sarcoma.

The symptoms were as follows. In case 1 (spindle cell fibrosarcoma) there were acute retention, rectal tenesmus and presence of a suprapubic mass. The prostate was large, firm, nontender in areas but not tender. In case 2 (pleomorphic fibrosarcoma) there were chills and fever, acute retention, lumbar pain on the left side and loss of weight. The prostate was markedly enlarged, symmetric, boggy and tender. In case 3 (rhabdomyosarcoma) there were perineal pain and acute retention. The prostate was enlarged, smooth, partially fixed but not hard. In case 4 (reticulum cell sarcoma) there were frequency of urination, nocturia and acute retention. The left lobe of the prostate was enlarged, soft and boggy but not tender.

The patients all died. In case 1 (spindle cell fibrosarcoma) death occurred eight months after onset of symptoms and seven months after operation and radiotherapy. In case 2 (pleomorphic fibrosarcoma) death occurred two months after onset of symptoms and five weeks after operation and radiotherapy. In case 3 (rhabdomyosarcoma) death occurred one year after onset of symptoms and two months after the first operation and implantation of radon seeds. In case 4 (reticulum cell sarcoma) death occurred six months after onset of symptoms and four months after the first operation and radiotherapy.

A review of the literature shows the following facts. 1. Sarcoma of the prostate is rare. Its incidence was approximately 1 in 1,000 prostates removed for "benign hypertrophy" or for carcinoma. 2. About 200 cases of sarcoma of the prostate have been reported to date. 3. While

sarcoma of the prostate tends to be a disease of youth and carcinoma a disease of later decades, nevertheless in rare instances carcinoma (usually one of the anaplastic types) does occur earlier than the fourth decade, and sarcoma (usually leiomyosarcoma or lymphosarcoma) may occur sometimes in the fifth to eighth decades. 4. Sarcoma of the prostate develops insidiously and painlessly but soon grows rapidly, breaking all barriers and causing obstruction. Operative procedures, except for the removal of obstruction, even accelerate the process, radiotherapy often gives relief.

Resection—Emmett⁴¹ states that it has been demonstrated that transurethral resection properly done can care for any and all types of obstruction of the vesical neck and that the functional results will be as good as or better than those produced by open types of operation.

Various instruments have been designed in the past for transurethral resection. One by one they gradually have been discarded until today two chief types remain in use. These are (1) the wire loop, activated with a high frequency cutting type of electric current and associated with a toroblique telescopic lens system, and (2) the cold punch instrument, which cuts with a cold tubular knife and does not have any telescopic equipment. Adequate and satisfactory operations can be done with either of these instruments if the surgeon is trained sufficiently in their use. Each instrument has its advantages and its disadvantages. The McCarthy resectoscope with its telescopic lens system furnishes a larger field of vision than the cold punch instrument and supplies moderate magnification of the operative field. The cold punch, on the other hand, allows only a relatively small field of vision, so that the instrument must be rotated through an arc of 360 degrees if one is to visualize the entire circumference of the prostatic urethra. To men trained in this type of direct cystoscopy, however, the limitation described does not present any particular problem, and any disadvantage is offset by the fact that in the presence of sharp bleeding the view is much clearer than that obtained with a lens instrument.

Experience at the Mayo Clinic with a large number of resections indicates that low spinal anesthesia is the anesthesia of choice. Procaine hydrochloride is used in doses of 70 to 90 mg dissolved in 2 cc of spinal fluid and is injected through the third or the fourth lumbar interspace. This yields sufficient anesthesia in the

40 Melicow, M. M., Pelton, T. H., and Fish, G. W. Sarcoma of the Prostate Gland. Review of Literature, Table of Classification, Report of Four Cases, *J. Urol.* 49: 675-707 (May) 1943.

41 Emmett, J. L. Transurethral Resection with the Cold Punch. Operative Technique, *J. Urol.* 49: 815-839 (June) 1943.

region of the prostate for at least sixty minutes, which is the maximal length of time any resection should take. Resection of small amounts of tissue or secondary resection often can be done while the patient is under intravenous anesthesia. At the Mayo Clinic the use of tracheal and caudal anesthesia has been discontinued in these cases because paralytic and occasionally systemic reactions from the rather generous amount of procaine hydrochloride employed have been annoying.

The remainder of Lammert's paper is limited to a consideration of the technique employed in transurethral prostatic resection with the cold punch.

Ninety per cent of all difficulty encountered in passing instruments through the male urethra which is not the site of a stricture is encountered at the apex of the prostate. When the urethra is enlarged by a benign or a malignant growth the chance of difficulty in this region is increased many-fold. To avoid errors of direction while introducing the resectoscope, one must be extremely gentle and slow in one's manipulative motions. A finger introduced into the rectum as a guide often will allow the surgeon to appreciate the situation. A Van Bincin sound carefully introduced may pass when a resectoscope will not, as the curve of the sound more closely simulates that of the urethra.

The actual mechanics of cutting tissue with the cold punch is quite simple. Although there are a few refinements of technique which are helpful to know. With the tubular knife in the closed position and the water inlet open, one observes the portion of tissue to be cut. The knife blade is then opened its entire distance (unless for some reason a shorter bite is desired) and the resectoscope is advanced sufficiently to allow the tissue to enter the fenestra. An attempt is made to fill the lumen of the resectoscope almost completely with the tissue so that the piece of tissue cut will be of generous size. The knife is then thrust forward, cutting off the piece of tissue. When the knife is opened again, the piece of tissue will be dislodged and in most cases will fall free into the bladder.

An adequate supply of sterile water is essential in transurethral resection. The source of water should be sufficiently high to allow the water to flow rapidly and adequately through the resectoscope, keeping it free of blood, so as to allow clear vision.

Many of the complications that follow transurethral resection can be attributed directly or indirectly to excessive loss of blood. For this reason it is imperative that hemostasis be main-

tained as perfectly as possible. With the activated loop type of resection, some hemostasis is secured with each cut. With the cold punch, each cut is made with a cold knife, and hemostasis must be secured subsequently by fulguration of individual bleeding points with the fulgurating electrode. Loss of blood may occur during operation and after operation. The periods are equally important. A good rule to follow is to control the bleeding fairly well in any region before proceeding to another.

It is a fairly common experience for the surgeon to note in the course of a resection that the wash water contains a large amount of blood and yet not be able to see where the blood is coming from. The bleeding eventually will be found to be coming from one or two large hidden spurting vessels. They are hidden usually by a piece of tissue which is situated near the apex. The most common site for these poorly visualized bleeding points is in the anterior sector near the apex. A small "roll" of adenomatous tissue situated adjacent to the external sphincter may obscure the origin of the bleeding vessel completely. Whenever such a situation is encountered the surgeon should remove the obstructing tissue at the apex quickly so that he has an unobstructed view of the entire region of resection.

The secret of good hemostasis in general surgical practice is adequate exposure. This is equally true in transurethral operations. There is nothing more difficult than to secure adequate hemostasis in an irregular, incompletely resected prostatic urethra in which there are alternate projections and depressions. Adequate exposure of the walls of the prostatic urethra, leaving a smooth, uninterrupted surface, permits complete and accurate visualization of all bleeding vessels.

Control of arterial bleeding usually does not present any difficulty. The same may be said of bleeding from small or moderate-sized veins. There is usually no difficulty in identifying the location of these veins unless there is some mechanical interference, such as remaining nodules of tissue, that obstructs the surgeon's view. This is not true, however, in the case of bleeding from large veins and venous plexuses. This type of bleeding is encountered when the resection is carried a little too deeply into the prostatic "capsule" or when the trigone is elevated or the muscle fibers at the vesical neck are incised too deeply. No "spurting" vessel is seen. There is rather a "welling up" of dark venous blood from a more or less deep cavity. In many such cases persistent fulguration tends only to enlarge the cavity and increase the hemorrhage. Another variety of severe venous bleed-

ing occurs in cases in which it appears as though definite coarse fibers of the prostatic "capsule" have been exposed and a "sheet" type of bleeding occurs from between them

If the posterior vesical lip has been cut so deeply that the trigone is separated from the vesical neck or becomes elevated, severe venous bleeding may occur from underneath the trigone. When one is examining this region, pressure with the heel of the resectoscope may tend to stop the bleeding so that the surgeon is unable to determine its source. Pressure of the resectoscope as one moves the instrument from place to place for observation may be sufficient to stop the flow of blood so that it is overlooked easily. This is especially true if the site of bleeding is near the apex, where the prostatic urethra is narrow. Here the slightest movement of the resectoscope to visualize a region may produce sufficient pressure to stop the bleeding temporarily. In such a case the bladder should be emptied completely and the resectoscope should be withdrawn to the distal border of the verumontanum, then the instrument should be kept in the midline and should not be moved from one side to the other, and the water should be allowed to run through the resectoscope very slowly. In this position the resectoscope may be rotated through an arc of 180 degrees. Usually, this maneuver will permit the surgeon to identify the site of the bleeding.

After a reasonable amount of fulguration has failed to control this type of bleeding, one should use a hemostatic bag catheter with or without tension. It goes without saying that if pressure can be exerted in the proper place the hemorrhage can be stopped. If the prostatic cavity is small and the bleeding is near the apex, a bag catheter distended with about 30 cc of fluid and pulled well down into the prostatic cavity should control the bleeding. If the prostatic urethra is large or if the bleeding is near the vesical neck, a larger bag, such as the pear-shaped Bardex bag, may be required. This bag may be distended with 120 cc or more of fluid. The bag often will fit well enough into the prostatic capsule to control the bleeding. At other times a moderate amount of traction may be necessary.

It must be remembered that a bag catheter will not control arterial bleeding. It is of value only in the presence of venous hemorrhage. In the absence of arterial bleeding a failure of the bag to control venous hemorrhage means that adequate pressure is not being obtained. In subtrigonal bleeding, for instance, owing to the laxity of the base of the bladder, no amount of pressure of a bag in the vesical neck may be effective

unless counterpressure can be applied against the base of the bladder.

The ease with which the patient may be cared for after resection depends chiefly on how perfectly hemostasis was obtained at the conclusion of the operation. The chief problem is to keep the catheter draining well in order that the bladder may be kept free of clots by lavage.

If the bladder becomes filled with clots and the catheter becomes obstructed, or if the bleeding continues to be too profuse, one should never hesitate to return the patient to the operating room to evacuate the clots and fulgurate the bleeding vessels. Pentothal sodium is usually the anesthetic of choice for such a procedure. No matter how full of clots a bladder may become, it should never be necessary to perform suprapubic cystostomy to evacuate them. The no. 28 F direct vision cystoscope or the resectoscope is inserted into the bladder, and the clots are aspirated by means of the suction syringe. After each aspiration a moderate amount of water is allowed to enter the bladder to furnish sufficient fluid to wash out the clots. Clots often tend to collect in the dome of the bladder and around the anterior half of the vesical neck. To remove such clots the resectoscope should be rotated so that the heel of the instrument is situated anteriorly. The ocular end of the resectoscope is then depressed so that the heel of the instrument is in the mass of clots. Aspiration with the suction syringe will then remove almost all of the clots.

Mercier⁴² describes the evolution of his ideas on the indications for transurethral resection of the prostate. Of the first 25 patients, 8 died, between the twenty-sixth and the one hundred and fiftieth patient 9 died, between the one hundred and fiftieth and the three hundredth 8 did not survive, between the three hundredth and the five hundredth 5 patients were lost, and in the last series, from the five hundredth to the nine hundredth, 3 died, a rate of 0.7 per cent.

Mercier uses McCarthy's resectoscope in conjunction with Wappler's cutting machine. In his opinion, all instruments are good, the solution lies in the skilful handling of one or the other. With McCarthy's, he is able to remove the hypertrophic tissue as far as the capsule without being obliged to insert the finger in the rectum so as to elevate the tumor and apply Stern's modified apparatus.

Spinal anesthesia was applied in 491 cases, patients were given cyclopropane with Connell's

42. Mercier, O. End Results of Nine Hundred Transurethral Resection of the Prostate. *Ann Surg* 49: 665-668 (May) 1943.

closed apparatus in 402. As regards the latter, in Mercier's opinion, there was little danger of explosion—he had installed a ground wire, and the anesthetist took great care to control any gas leak. Seven patients who had "grade A" prostates were anesthetized with pentothal sodium.

Mercier states that the tendency of beginners is to overcoagulate, both as to area and as to depth, in order to avoid hemorrhages in the course of the operation. If coagulation is excessive, grave secondary hemorrhages may happen about the tenth or twelfth day after the resection, moreover, elimination of coagulated tissues will impede recovery. Mercier coagulates superficially at the precise point where an artery bleeds, and he avoids coagulation of veins except when there is considerable hemorrhage. After a trial of compression catheters, they were abandoned, because they are useless if coagulation has been obtained properly and also because they frequently cause painful vesical tenesmus. He uses Marion's rubber catheter, which furnishes the advantage of multiple outlets. He lets it remain for three days, but in cases in which fever runs high, he does not remove it until the temperature has fallen to normal. On the day following the operation, he prescribes sulfonamide medication. This clarifies the urine and brings it back to normal within a period that varies between fifteen days and eight weeks. The same results are obtained in pollakiuria.

The quantity of tissue taken out in these 900 cases varied between 2 and 182 Gm. The length of time that it took to perform transurethral resection stretched from three to sixty-five minutes, the latter in the case in which tissue weighing 182 Gm was resected. In all of these cases Mercier never had recourse to a two stage operation but removed in one session the quantity of tissue deemed necessary. In 11 instances he used transurethral resection after cystotomy, but since then he has abandoned this practice.

One hundred and twenty-four patients (13.8 per cent of the 900) presented carcinoma of the prostate. The 776 remaining patients presented benign hypertrophy of the prostate. Four hundred and eighty-two patients answered a questionnaire. Of these 482 patients 9 had to undergo a second operation. Four of them, on whom a first operation had been performed in 1934, underwent a second operation in 1936. Two underwent a first operation in 1936, 1 in 1937 and 2 in 1939, a second operation was performed on each of these 5 patients in the course of the same year, respectively. The probable cause of each of these reiterations seems to have been that not enough tissue was removed in the first instance.

In these 482 cases pollakiuria and urinary pains never lasted more than eight weeks, and in 296 of the cases these troubles had disappeared within the month following the operation. Finally 182 patients retained pollakiuria, which returns once in the latter part of the night.

Davis⁴³ states that during the past decade there has been an extraordinary change in the attitude and opinion of members of both the laity and the medical profession with respect to prostatic surgery. The factors responsible for this may be enumerated as follows: (1) the gradual recognition that the tradition that prostatectomy is a hazardous ordeal is fallacious, (2) the development and more frequent use of transurethral prostatic resection, (3) articles on genitourinary subjects in popular lay magazines, (4) syndicated newspaper articles by reputable medical columnists, (5) ethical "public enlightenment" programs, sponsored by medical societies, (6) "protect your health" magazine advertisements sponsored by life insurance companies, (7) persistent blatant radio advertisement by utterly unscrupulous charlatans, (8) the introduction of the sulfonamide group of antiseptics of the urinary tract, and (9) what may be termed the modern tendency toward lay enlightenment.

For these reasons the urologic surgeon now sees a much larger percentage than he did formerly of patients for whom the risk of operation is low, permitting safe prostatic operations without preliminary drainage. However, even with this increase surgeons are not seeing a great many such patients.

Osteomyelitis Complicating Prostatic Operations—Deming and Zaff⁴⁴ discuss metastatic vertebral osteomyelitis complicating prostatic operations and report 3 cases which illustrate a definite relation between infection of the urinary tract and acute vertebral osteomyelitis.

In a series of 1,500 cases of pyogenic osteomyelitis, it was found that the spinal column was involved in 3.94 per cent. Acute pyogenic spinal osteomyelitis is infrequent among persons of the ages at which involvement of the prostate is common. The average age for osteomyelitis of the spinal column is 31 years. Men are affected twice as often as women. The location of spinal osteomyelitis was coccygeal in 3 of 102 cases, sacral in 9, cervical in 8, thoracic in 31 and lumbar in 51. In another series of 71 reported cases, the location was sacral in 9, cervical in 12,

⁴³ Davis, E, in discussion on Mercier,⁴² p. 672.

⁴⁴ Deming, C. L., and Zaff, F. Metastatic Vertebral Osteomyelitis Complicating Prostatic Surgery, *Tr. Am. A. Genito-Urin. Surgeons* (1942) 35: 287-305, 1943.

thoracic in 19 and lumbar in 31. Thus there is a predilection in the lumbar region for this lesion.

The symptom complex of acute osteomyelitis of the spinal column is clinically dramatic. It is characterized by rigors, high fever, prostration, delirium, abdominal distention and diarrhea. Marked leukocytosis is usually present. The local pain and the neurologic manifestations frequently suggest the site of the lesion. Blood cultures are frequently positive. Many reports of cases of acute osteomyelitis of the spinal column contain a reference to the high percentage of cases in which there is infection of the urinary tract. Carson reports 4 cases of acute osteomyelitis of the spinal column and states that there were two factors common to all: *Staphylococcus aureus* septicemia and infection of the urinary tract. The general symptoms may be acute or subacute, and some days may elapse before local signs appear. Movement usually causes pain. In 3 cases presented by Deming and Zaff, pain in the back occurred on the fourth and fifth postoperative days, respectively, in the first 2 cases and on the eighth postoperative day in the third case. The mortality rate in cases of acute spinal osteomyelitis varies from 25 to 71 per cent.

The essential diagnostic features of the cases presented were narrowing of the intervertebral spaces, irregular destruction of adjacent portions of the vertebral bodies, varying degrees of sclerosis of the participating vertebrae and rapid proliferative periosteal formation of new bone. The presence of an associated paravertebral shadow of soft tissue tends to confirm the diagnosis. These findings coincide with the accepted roentgenologic appearance of pyogenic osteomyelitis of the spinal column.

The invasion producing acute pyogenic osteomyelitis of the vertebrae has been recognized as (1) direct and (2) hematogenous. In only 3.94 per cent of 1,500 cases of acute pyogenic osteomyelitis did lesions of the spinal column develop, so that infection does not spread through the blood stream from one bony lesion to another often. Infection of the blood stream is common, but acute vertebral osteomyelitis is rare. The so-called typhoid spine and gonococcic arthritis of the spinal column have been explained on a blood-borne basis. Many patients suffering from typhoid have infection of the urinary tract.

In all 3 of the cases of prostatic resection presented, acute spinal osteomyelitis developed following operation. In 2 of the cases the classic two stage suprapubic operation, and in the third, transurethral resection, was performed. There was nothing in the histories to indicate that such

a complication as metastatic vertebral osteomyelitis should be expected. All 3 patients showed certain postoperative symptoms in common. The immediate convalescence was usually stormy and severe. All had chills and "spiking" temperatures in spite of the administration of urinary antiseptics and the large intake of fluid. All 3 patients suffered from weakness or prostration, perspiration, abdominal distention, hiccup, restlessness and irritability.

The early treatment of the severe backache in the 3 patients could have been improved if the correct diagnosis had become apparent. However, conservative therapy was naturally applied. Roentgen therapy, given in the first case, did not give a satisfactory result. In the second case, rest and the wearing of a back brace were prescribed, with a satisfactory result, after the exact diagnosis had been made. Surgical exploration clarified the diagnosis in the third case, but the disease was too far advanced for recovery to be expected. Patients who have undergone prostatic resection and who complain of severe backache complicating their convalescence should be suspected of having early vertebral osteomyelitis, and treatment should be instituted to prevent extension of the pathologic process, to shorten the period of convalescence and to diminish the mortality rate. Any infection of the urinary tract represents a potential factor for the development of metastatic vertebral osteomyelitis.

Kretschmer,⁴⁵ in discussing the article of Deming and Zaff on metastatic vertebral osteomyelitis complicating prostatectomy, states that he has seen 3 patients who had metastatic osteomyelitis of the spinal column. The first patient was a man who had a single kidney and who was operated on for a stone in the ureter, which was removed successfully. Several months prior to this operation, he had had nephrectomy for pyonephritis. Following the removal of the stone, severe pain developed in the back, and a low grade fever was noted. Physical examination disclosed interference with the function of the spinal column in that it was impossible for the patient to flex it. A roentgenogram showed osteomyelitis. This healed with rest in bed.

The second patient was a man who had been operated on four weeks before he came to Kretschmer. The diagnosis made prior to operation was perirenal abscess. At operation no perirenal abscess was found. The patient complained of pain in the back, a low grade fever and leukocytosis. He, too, was unable to flex

⁴⁵ Kretschmer, H. L., in discussion on papers by Cahill, Melicow and Guerry,⁵⁶ Kretschmer, Deming and Zaff,⁴⁴ McCague²⁹ and Paine, *Tr. Am. A. Genito-Urin. Surgeons* (1942) **35**: 320-321, 1943.

his spinal column. A roentgenogram disclosed vertebral osteomyelitis. Rest in bed and appropriate orthopedic treatment with splints and braces resulted in a complete cure.

In the third case metastatic vertebral osteomyelitis developed following prostatectomy.

Kretschmer expressed the opinion that in the cases just cited the infection was metastatic.

URETHRAL DIVERTICULUM

Higgins and Roen⁴⁶ state that urethral diverticulum is rather uncommon among women, although exact statistics as to its frequency are not available. At the Mayo Clinic 19 cases were encountered in a ten year period. At the Cleveland Clinic only 7 cases, including the one reported by Higgins and Roen, have been observed in the twenty-two years since 1921.

Urethral diverticulum may be defined as a pouch formed by dilation of a portion of the urethrovaginal septum and communicating with the urethral canal. The pouch may communicate widely with the urethra, or it may have a narrow or tubular opening into it.

It is quite likely that the true congenital diverticulum of the urethra more often presents features that simulate cystocele than do those sacs which arise secondarily. There are two principal causes of the acquired type. 1 Trauma may produce a weakened point in the urethral wall, and herniation may later occur through this region. Trauma may be in the form of passage of a calculus, instrumentation or childbirth. Undoubtedly, the last is the most frequent causative factor. Instrumentation is not so often the cause in the female urethra as in the longer pendulous urethra of the male sex. 2 An inflammatory process in the periurethral tissues may serve to produce a diverticulum. Inflammatory occlusion of a urethral duct may produce a retention cyst of the associated gland, and subsequent suppuration and rupture into the urethral lumen may serve by repetition to produce an increasingly larger sac.

The symptoms of urethral diverticulum with or without calculus are those of infection of the lower part of the urinary tract, including frequency and dysuria, nocturia, pyuria and rarely hematuria, and in instances in which the calculus is large, urethral obstruction may occur. Local examination reveals a smooth spherical visible and palpable swelling of the anterior vaginal wall just posterior to the external urethral meatus. This must not be confused with cystocele. If a

calculus is present, this swelling is hard. Urethroscopic inspection and roentgenographic examination, especially if a cystogram has been made with a urethral catheter in place, confirm the diagnosis.

The treatment of urethral diverticulum with or without stone is entirely surgical. The sac of the diverticulum is approached readily through incision in the anterior vaginal wall. Resection of the sac with resuture of the urethral and vaginal walls has given universally satisfactory results. Diversion of the urinary stream for approximately a week is a necessary feature of the treatment. In most cases this may be accomplished by an indwelling catheter, rarely, suprapubic cystotomy may be required. In all reported cases the wall has healed promptly without the formation of a urethrovaginal fistula.

Higgins and Roen report the case of a woman aged 66 years, who complained of dysuria, frequency, difficulty in voiding and slight terminal hematuria. The past history was irrelevant except for the fact that some three to four years previously she had experienced a severe attack of "cystitis" which had subsided in a month's time. The present urinary symptoms had appeared about eight months prior to her visit to the clinic. The symptoms had been progressive, especially the difficulty in voiding.

Physical examination revealed a somewhat obese elderly woman who did not show any abnormality except for a bulging hard mass in the anterior vaginal wall. This was diagnosed clinically as a calculus within a diverticulum of the urethra.

Roentgenologic study disclosed a large calculus below the level of the bladder. The urogram indicated that the upper part of the urinary tract was normal. Urinalysis revealed a number of white blood cells and red blood cells. Culture of the urine showed *Bacillus coli*.

At operation the anterior vaginal wall was incised longitudinally, the diverticular sac was opened and the calculus extracted. The sac was then excised and the orifice into the urethra closed by a purse string suture. This orifice was quite narrow with a diameter of approximately 5 mm. The vaginal wall was sutured. A catheter was left indwelling for six days after operation. The wound healed by primary intention, and the patient returned home eleven days after operation, free of symptoms.

The calculus was large measuring 3.9 by 2.6 by 2.5 cm, and was smooth hard and laminated, with a soft center. Chemical analysis showed it to be composed of calcium phosphates carbonates and a trace of ammonia.

46 Higgins, C. C. and Roen, P. R. Calculus-Containing Urethral Diverticulum in a Woman. Report of a Case, *J. Urol.* 49:715-719 (May) 1943.

TESTICLE

Prosthesis—Rea⁴⁷ reports a case in which an artificial testicle made out of lucite (polymerized methyl methacrylate) was implanted in the scrotum of a boy 13 years of age who was believed to have congenital anorchidism. The cosmetic and psychic results of the operation justified the procedure. Lucite spheres have been implanted in the scrotum also in a case of orchidectomy for a malignant tumor of the testis and also in 2 cases of castration for carcinoma of the prostate. A note is made concerning the size of testes at different ages, and some impressions concerning the size of artificial testicular implants are recorded.

Polyorchidism—Thiessen⁴⁸ states that the presence of more than two testes in man is a rare occurrence. In the older literature there are numerous, almost mythologic references to warriors and lovers who were thus endowed. Few proved cases have been reported. Thiessen adds 1 more proved case to the literature.

The patient who was 25 years of age, complained of a pain in the right inguinal region. Twelve years before, following trauma, the right testicle, which had been normal in size, decreased somewhat. The left testicle was normal. Shortly after this right inguinal hernia developed. The results of general examination were negative except for relaxed bilateral external inguinal rings. The right testicle was atrophic. Surgical repair of the hernia was advised. At the time of operation the right side was explored first. A thickened cordlike structure was felt separate from the spermatic cord and the vessels. The upper end continued retroperitoneally to a rounded mass resembling a testicle. The scrotal testicle was found and delivered into the incision. Its vessels and cord were separate from those of the intra-abdominal organ. The smaller, upper testicle was removed. Microscopic examination showed testicular tissue.

EPIDIDYMIS

Blastomycosis—Jacobson and Dockerty⁴⁹ describe the clinical and pathologic features of 4 cases of systemic blastomycosis involving the epididymis. Epididymitis was the most common genitourinary manifestation of blastomycosis, in

the series of cases of generalized blastomycosis observed by Jacobson and Dockerty the incidence was 33 per cent. Clinically the condition simulated tuberculosis. A primary pulmonary focus was established definitely in 1 case, and such a focus was believed to be present in 2 additional cases. In the remaining case evidence of intrathoracic disease was not obtained at necropsy. Treatment with iodides and irradiation apparently was successful in 2 patients, who survived for two and ten years, respectively. One of these patients had undergone epididymectomy, which apparently hastened recovery. In 2 patients the disease proceeded to a fatal outcome, with involvement of the genital structures in the terminal stages of the disease.

Tumor—Evans⁵⁰ describes a group of tumors, benign in character and of characteristic histologic structure, located in direct relationship to the tunica vaginalis testis and the epididymis, including 5 personally observed and a larger number assembled from the literature. It is concluded that the tumors of this group probably are derived histogenetically from the mesothelial cells of the serosa of the tunica vaginalis and may properly be denominated mesotheliomas.

AVULSION OF SCROTUM

Byars⁵¹ reports 3 cases of avulsion of the scrotum and of the skin of the penis. In each instance avulsion was the result of loose clothing being caught in rapidly moving machinery. Such defects of the genitalia are rather rare.

The scrotal flap with pedicle supplies the most desirable tissue for covering a penile defect because of the elasticity of the transplanted skin. This is especially true when there has been damage to the corpora cavernosa with deep scarring and contraction. In many of these cases scrotal tissue is not available since it also has been lost. Even under ideal circumstances the scrotal tissue may be inadequate in amount for complete coverage of the penis. A third point to be considered is that a wound of the penis which has contracted may undergo further contraction during the period of attachment of the penis to the scrotal flap. Pedicled flaps from other portions of the body are too thick and lack the desired elasticity.

Thick split skin grafts seem to answer most nearly the needs in the average case. If possible, it is oftentimes desirable to use a combination of scrotal flap and free skin graft, especially to prevent possible scar constriction about the base.

50 Evans, N. Mesothelioma of the Epididymis and Tunica Vaginalis, *J Urol* 50:249-254 (Aug.) 1943.

51 Byars, L. T. Avulsion of Scrotum and Skin of Penis, *Surg, Gynec & Obst* 77:326-329 (Sept.) 1943.

47 Rea, C. E. The Use of a Testicular Prosthesis Made of Lucite, with a Note Concerning the Size of the Testis at Different Ages, *J Urol* 49:727-731 (May) 1943.

48 Thiessen, N. W. Polyorchidism—Report of a Case, *J Urol* 49:710-714 (May) 1943.

49 Jacobson, C. E., Jr., and Dockerty, M. B. Blastomycosis of the Epididymis. Report of Four Cases, *J Urol* 50:237-248 (Aug.) 1943.

of the penis. The difficulty of "take" in this area makes the free full thickness graft less desirable than the split skin graft. The disadvantages of the free skin graft are that the skin is not as expansile as is normal penile skin and that the grafts tend to contract for a period after their application. Both of these difficulties may be largely overcome by the transplantation of an adequate amount of skin. This is done by making the wound the maximal size at the time of application of the graft and by supplementing the graft if necessary at a second operation.

In the preoperative preparation of an ulcerated wound, all surrounding hair should be kept shaved, the area should be cleansed frequently by the use of soap and water and sulfanilamide or sulfathiazole powder should be dusted on the surfaces one or more times daily. The patient sits in a saline bath for several hours daily if possible. When the granulations have become compact and uniformly red, and there is a minimum of discharge on the dressings, and the appearance of the wound has ceased to improve, the wound is ready for grafting.

At the time of repair, all granulation tissue is trimmed away with a sharp knife, and the deeper scar is dissected away carefully until the penis is completely elongated and freed from the contraction which has resulted from partial healing. All bleeding points are ligated carefully with the finest available silk. If there is any normal skin left on the penis, either about its base or about the glans, this skin is retracted. A collar of skin about the base of the penis can be sutured back as a roll at its junction with the abdominal wall. A collar of skin about its attachment to the glans can be drawn toward the tip of the penis.

For a split skin graft, approximately two thirds of the thickness of the skin is taken. If it is possible to get one piece large enough to cover the entire wound, this is done. A catheter is inserted into the bladder, and the penis is held completely extended. The graft is draped over the wound and sutured accurately to the borders of the wound proximally and distally, with interrupted sutures.

The first postoperative dressing of the wound is done on the fourth or the fifth day after operation. A dressing as nearly like the original as possible is reapplied. After the seventh or eighth postoperative day the catheter is removed. A similar but less bulky dressing is applied and is held in place with an athletic supporter. Split skin grafts undergo a period of contraction during the first two months. Following this, they begin to soften and relax.

Byars presents these cases with the idea of expressing the desirability of primary repair

rather than subjecting the patient to the prolonged discomfort coincidental with secondary repair. In addition, he feels that grafting of skin to properly prepared open wounds resulting from avulsion of tissue is practical and should be considered even though a number of hours have elapsed since the injury.

In none of Byars' 3 cases was restoration of the scrotum attempted. It is obvious that under some circumstances such a reconstruction might be considered essential. If it is contemplated, the testicles should be planted under the skin and the subcutaneous tissue of the upper inner parts of the thighs at the time of the initial repair. After the defect of the penis has been repaired adequately and has healed, each testicle and its cord would be dissected free from the thigh, carrying with it the overlying skin and fat. The tissue from the right and the left thigh then would be sutured together in the midline, the testicles with their overlying skin and fat being joined to make the two halves of the reconstructed scrotum. This would occupy approximately the normal position and probably would maintain nearly the optimal temperature of these organs. This reconstructed scrotum would not be contractile. The two donor sites on the inner surfaces of the thighs would be covered with split skin grafts.

SPERMATIC CORD

Tumor—Zide⁵² states that the occurrence of tumor of the spermatic cord is relatively rare in comparison with tumors of other structures of the body. In 1939 Schulte reported 247 cases of tumor of the spermatic cord. Since that report 10 additional cases, including the case reported now by Zide, have been compiled, bringing the total to 257 cases. Classifying these cases further, he notes that the most common types of tumor were lipoma, sarcoma, fibroma, mesodermal tumor, dermoid and angioma in decreasing order of frequency. Only 4 cases of hemangioma have been reported hitherto. Zide reports the fifth case of hemangioma of the spermatic cord. This case is of interest because of the rarity of the tumor and the problem of differential diagnosis.

A man aged 27 years had had a tumor in the right side of the scrotum for sixteen years. The mass was tender to palpation and ached on exertion. On examination the scrotum was enlarged slightly at the right upper portion. There was a lobulated mass, 2 by 3 cm in diameter, just above the right testis. It did not transilluminate, and there was no noticeable change of size when the patient reclined. The tumor was excised through an incision in the upper right area of the

52 Zide, H. A. Tumors of the Spermatic Cord. Report of a Hemangioma, *J Urol* 50:255-257 (Aug) 1943.

scrotum, approximately 1 cm of the spermatic veins above and below its boundaries being removed. The diagnosis was hemangioma of the spermatic cord.

INFECTIONS OF THE URINARY TRACT

Discussing infections of the urinary tract, Cook⁵³ states that since the development of sulfonamide compounds with their known efficacy in combating infections of the urinary tract, many physicians have prescribed these drugs without sufficient knowledge of the infectious bacteria in the given case, without knowledge of the true pathologic changes and without proper respect for the various toxic manifestations which may develop in the patient.

Complete bacteriologic studies are not necessary in each case by any means. A simple Gram stain of the urinary sediment, which is at the disposal of any surgeon, will usually suffice and lead to the proper management of the patient. Cultures are helpful but are not always necessary.

Many patients may be cured of their illness with chemotherapy, as their difficulty is superficial. However, if after one or two courses of medication the desired results are not obtained, the patient is entitled to a detailed urologic investigation. The percentage of cures in cases of infection of the urinary tract falls sharply when one passes from uncomplicated to complicated infections.

When considering the drugs themselves, one should not lose sight of the value of mandelic acid. It should not be used in cases of impaired renal function, as in such cases it is toxic to the kidney. Concerning the sulfonamide compounds, there is a definite need for continued and close observation while the patient is taking the drug.

If everything possible is to be secured from chemotherapy in infections of the urinary tract, a close check on each patient must be kept. Doses should not be excessive. Repeatedly it has been demonstrated experimentally that small concentrations of any of these drugs will sterilize the urine. This has been borne out clinically. Seldom, if ever, will increased doses do more than will the usual small doses.

URINARY CALCULI

Lassen⁵⁴ states that there are two main groups of causes in the genesis of urinary calculi. One group, which undoubtedly is the more rare of the two, is that in which disease processes within or outside the urinary tract operate to supply the conditions requisite for the formation of calculi.

⁵³ Cook, E. N. Infections of the Urinary Tract editorial, Surg., Gynec. & Obst. 77:330-331 (Sept) 1943.

⁵⁴ Lassen, H. K. The Formation of Urinary Calculi, J. Urol. 50:110-120 (July) 1943.

The other group of causes, which is the more important group by far, consists largely in dietary insufficiency. Both these two groups of causes, which, as has been demonstrated, consist of a large number of various factors, can bring about changes in the saturation of the urine and, as a consequence, nuclei for the formation of calculi arise. Even though the original pathologic condition which caused these retained nuclei does not remain active, the nuclei themselves may continue to grow despite the fact that the urine is absolutely normal.

Sauer and Neter⁵⁵ report that favorable results obtained by the use of a citric acid-magnesium oxide-sodium carbonate solution (solution G, arrived at by Suby, Suby and Albright^{26b}, Suby and Albright^{26c}) in the treatment of patients who had late radium reactions, complicated by formation of incrustations, stimulated in vitro experiments on the antimicrobial action of this solution.

Solution G produced bactericidal effects within twenty-four to seventy-two hours at 37 C against strains of *Escherichia coli*, *Proteus vulgaris*, *Proteus morgani* and *Streptococcus faecalis* (enterococcus).

Young cultures of *E. coli* (four and ten hours old) were more susceptible to the bactericidal action of this solution than twenty-four hour cultures.

Admixture of urine in appreciable amounts to solution G caused increase of p_H and decrease of bactericidal activity against *Escherichia coli*.

Solution G exerted approximately the same bactericidal effects against *E. coli* as a citric acid-disodium phosphate buffer solution of identical p_H (4.0).

Solution G is made as follows:

Citric acid (monohydrous)	32.3 Gm
Magnesium oxide (anhydrous)	3.8 Gm
Sodium carbonate (anhydrous)	4.4 Gm
Distilled water in sufficient quantity to make	1,000.0 cc

THE RENAL LESIONS IN VON HIPPEL-LINDAU DISEASE

Cahill, Melicow and Guerry⁵⁶ discuss the renal lesions in von Hippel-Lindau disease and report a case.

Angiomatosis retinae was described first by von Hippel. Hemangioblastomas have been reported by various observers to occur associated

⁵⁵ Sauer, H. R., and Neter, E. The Bactericidal Action of the Stone Dissolving Agent "Solution G," J. Urol. 50:191-196 (Aug) 1943.

⁵⁶ Cahill, G. F., Melicow, M. M., and Guerry, D., III. The Renal Lesions in von Hippel-Lindau's Disease. Tr. Am. A. Genito-Urin. Surgeons (1942) 35:271-281, 1943.

with other lesions of the central nervous system. Lindau was the first to recognize that a generalized form of hemangioblastoma occurs, in which not only tumor of the retina may be observed but cysts of various viscera, with cystadenoma of the pancreas and hypernephroma of the kidney.

Lindau reported that hypernephroma was present in 6 of his 15 cases. Since it occurred in the case of Davidson and his associates, in that of Wolf and Wilens and also in the present case, the proportion has been increased to 9 of 18 cases, or 50 per cent.

The case reported by Cahill, Melicow and Guerry is of interest in that the patient showed the hormonal deficiency changes thought to be due to involvement of the pituitary gland. She did not have any demonstrable pancreatic cysts. Her large renal tumor was recognized and removed and was found to be a hemangioblastoma.

The patient was a white woman, aged 26 years, who complained that her vision had been failing for eighteen months. There had been no urinary symptoms of any character. At no time had hematuria occurred. For a number of months previous to admission she had had several attacks of dull pain in the right flank lasting for several days.

Retrograde pyelograms showed a deformity of the right renal shadow similar to that seen in cases of renal tumor. There was no evidence of metastasis in roentgenograms of the lungs. At operation, first the abdomen was explored through a transverse incision of the abdominal wall on the right side. There were no palpable cysts in the intestines, the pancreas, the liver, the spleen or the left kidney. The large right renal mass was removed transperitoneally with the perinephritic fat attached, after ligation and division of the renal vessels. Microscopic examination revealed hemangioblastoma.

This is an unusual neoplasm of the kidney. It differs in many respects from so-called hypernephroma or carcinoma of the kidney. In the first place there is a strong tendency toward formation of capillaries. Then again there is the frequent massing of "foam cells" between hemangiomatous regions. Correlating these findings in the kidney with the clinical picture presented by the patient, Cahill, Melicow and Guerry conclude that this was a case of Lindau's disease affecting the kidney.

PRESACRAL SYMPATHICOBLASTOMA CAUSING URINARY OBSTRUCTION

Hepler⁵⁷ reports the successful treatment of a presacral sympathicoblastoma. The patient was an infant, and the tumor caused urinary obstruction at birth.

The presacral position of the tumor was of interest because sympathicoblastomas are usually

primary in the adrenal medulla. However, the region ventral to the sacrum is a sort of repository or burying ground for remnants cast off in the complex embryonic development of the terminations of the intestinal tract and the central nervous system, and these remnants later may give rise to complex tumors. Included among these may be those which arise from the neurenteric canal, those from the postanal gut, the Middledorf tumors, sacral teratomas, chordomas and ependymomas.

Tumors arising from the formative cells of the sympathetic nervous system are usually primary in the adrenal medulla, but they do arise in the cervical, retropleural, retroperitoneal and sacral regions, and the histogenesis and the prognosis are the same for the extra-adrenal as for the adrenal growths.

Such a tumor was discovered filling the pelvis of a boy aged 3 weeks, who had been unable to urinate since birth. It arose from the hollow of the sacrum, compressed the urethra and displaced the bladder upward. It was partially removed through a midline abdominal incision, and the remnant disappeared after two months of roentgen treatment. There has been no recurrence during four years.

Histologic preparation showed the tumor to be malignant sympathicoblastoma. Tumors of this type are supposed to be radioresistant and highly fatal. The predominating cells were sympathicoblasts and sympathigonia, parent cells in the formation of the sympathetic nervous system. There were a few "rosettes," but otherwise there was little cellular differentiation. This fact indicates a high degree of malignancy.

The unexpected results in this case bear out Farber's contention that the prognosis is not hopeless. In his series of 40 patients 25 per cent were alive and well three to five years after the operative discovery of the tumor.

One is impressed by the unexpected results in one case of a treatment which has failed completely in another. Surgical removal followed by irradiation may fail in the treatment of a patient who has a tumor that has not metastasized and yet be successful in the treatment of another patient in whom there is demonstrable metastasis. The tumor may undergo spontaneous hemorrhage and necrosis and disappear without any other surgical intervention except biopsy. It may undergo maturation and develop into a benign ganglioneuroma. This process is comparable to the maturation which takes place in the development of the sympathetic nervous system.

Because of the unpredictable course of the process and of the response to treatment one is

⁵⁷ Hepler, A. B. Presacral Sympathicoblastoma in an Infant Causing Urinary Obstruction, *J Urol* 49: 777-784 (June) 1943.

justified in performing as complete a surgical removal as possible, to be followed by irradiation. The irradiation should be postoperative and not preoperative. Although these tumors rarely present a problem in urologic practice except in their differentiation from embryoma of the kidney, the possibility of their extra-adrenal origin must not be forgotten.

ANESTHESIA

Hess and Merski⁵⁸ state that pentothal sodium is the ideal anesthetic agent for short and long urologic procedures. It is the safest of all. The skilled anesthetist finds it easy to administer. The patient is ready for operation in a few moments after the administration of the anesthetic agent is started and is out of anesthesia in

⁵⁸ Hess, E., and Merski, A. T. Some Observations in the Use of Pentothal-Sodium, *Urol. & Cutan. Rev.* 46: 709-713 (Nov.) 1942.

a few minutes after the injection is stopped. He is comfortably drowsy the rest of the day.

This anesthetic agent can be used under all operative conditions, since it is nonexplosive, and it can be given time after time without any ill effects.

The pulse rate and the blood pressure are not influenced by pentothal sodium. If anything, it seems to improve the action of the heart in some of the cases in which concern is felt because of a damaged myocardium. The one danger is sudden respiratory failure. The antidotes for respiratory failure are oxygen, picrotoxin, coramine (a 25 per cent solution of pyridine beta-carboxylic acid diethylamide), metrazol and aromatic spirit of ammonia U. S. P.

Hess and Merski state that pentothal sodium in their hands has proved so safe that they consider it the best general anesthetic agent for all surgical purposes.

PERMEABILITY OF LYMPH VESSELS AND LYMPH PRESSURE

FERDINAND C LEE, MD

BALTIMORE

The purpose of this article is to present the results of experiments which were intended more to explore new avenues in the physiology of the lymph system than to give intensive study to individual aspects of a limited problem. At this writing it is uncertain when it will be possible to support by a longer series of experiments the conclusions obtained from relatively few pioneering observations.

It has long been known that ligation of the thoracic duct causes deposition of chyle in the retroperitoneal tissues. Whether this condition is due to a rupture of a lymph vessel¹ or whether it represents a transudation through an intact vessel wall² has never been decided. The first experiments were planned to shed light on this problem alone, but they soon presented other facets which invited exploration.

EXPERIMENTS

When the chyle-bearing thoracic duct of the cat is ligated in the chest according to a method described in 1922,³ the resulting deposition of retroperitoneal chyle reaches its maximum in from twenty-four to forty-eight hours. The extent of this chylous effusion is variable, but after maximal effusion the stomach is not covered, certainly never the liver, nor does the mass extend into the pelvis, even though small deposits may be seen along the proximal portion of the iliac vessels. At the end of seventy-two hours much of the extravasated chyle will have been absorbed, and it is rare for any trace of it to remain longer than one hundred and forty-four hours. The deposits in the distal portion of the mesentery, near the intestine itself, are among the first to disappear, whereas proximally

the tissue immediately around the intestinal lymph gland is among the last to surrender its chylous deposit. Usually there is a small amount of chylous ascites present by the end of twenty-four hours after ligation of the thoracic duct, however, in another twenty-four hours it is rarely possible to aspirate any more chylous fluid from the peritoneal cavity.

As regards these experiments, the most common site for the first signs of chylous extravasation following ligation of the thoracic duct in the cat was at the inferior border of the cisterna chyli above the pedicle of the left kidney. This observation was made in 7 animals.

In 2 cats the earliest appearance of the retroperitoneal chyle following ligation of the thoracic duct in the chest was in forty-five minutes. For the other 5 animals, the time of appearance was respectively fifty, sixty-five, seventy, seventy-five and eighty minutes. The procedure in the experiments was to open the abdomen thirty minutes after ligation of the duct in the chest, with the animal under intratracheal ether anesthesia, and after inspection of the left cisternal region to close the abdominal incision with towel clips, and to repeat the inspection every five minutes.

Once the retroperitoneal chyle had appeared at the cisterna chyli, it could be found around the intestinal lymph trunks and the mesenteric glands by the end of another fifteen minutes. The subsequent spread of the extravasated chyle in the mesentery toward the intestines became progressively slower.

It may be well to define some of the terms that will be used in the remainder of this article. The mesenteric lymphatics or lymph vessels are situated in the mesentery of the small intestine and conduct the lymph from the small intestine to the intestinal lymph gland situated at the root of the mesentery. This lymph gland is relatively large and conglomerate and should not be confused with the small lymph glands which are frequently found isolated within the mesentery of the small intestine. From the intestinal lymph gland several large lymph vessels, called intestinal lymph trunks, carry the lymph to the

From the Departments of Surgery and Anatomy of the Johns Hopkins University

1 Cooper, A. Three Instances of Obstruction of the Thoracic Duct, with Some Experiments Showing the Effects of Tying That Vessel, *M Rec Private M A*, 1798, p. 86.

2 Schmidt-Muhlheim, A. Gelangt das verdaute Eiweiss durch den Brustgang in's Blut? *Arch f Anat u Physiol (Physiol Abt)* 1877 p. 549.

3 Lee, F. C. The Establishment of Collateral Circulation Following Ligation of the Thoracic Duct, *Bull Johns Hopkins Hosp* 33 21, 1922.

cisterna chyli, which in turn discharges its lymph into the thoracic duct

While the fluid element of the lymph was thus leaving the vessels, the question naturally arose as to the fate of the lymphocytes within the lumens of the lymph channels. The entire trunks of 7 animals were immediately placed in a 4 per cent solution of formaldehyde at the end of the experiment, and subsequently histologic sections

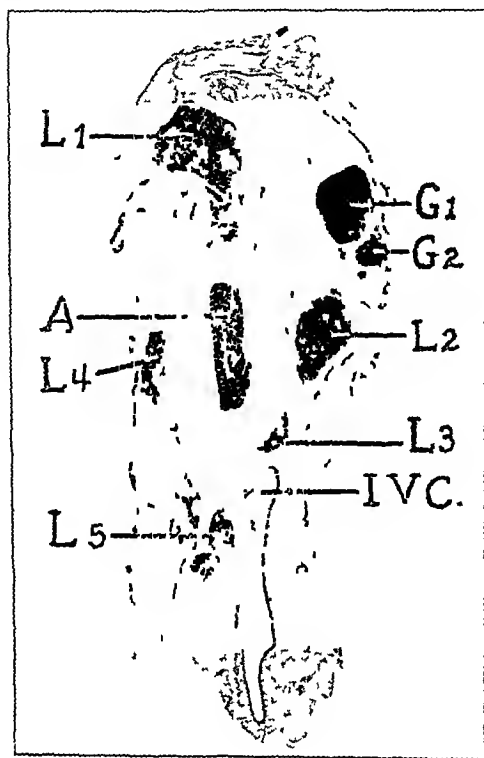


Fig 1—Cross section of the posterior abdominal wall of a cat whose thoracic duct had been ligated in the chest three hours previously to show the concentration of lymphocytes outside of lymph vessels in areas L1 to L5 inclusive, in comparison with lymph glands G1 and G2. A, aorta, IVC, inferior vena cava. The area L1 is shown enlarged in figure 2. Hematoxylin and eosin stain $\times 10$.

were obtained from various areas, beginning at the point of ligation of the thoracic duct in the chest and continuing down to the lower portion of the abdominal aorta. Blocks were also obtained from the region about the intestinal lymph trunks. All the sections were cut from celloidin-embedded blocks and were stained in hematoxylin and eosin.

It was found that in 5 of the 7 animals the highest concentration of lymphocytes occurred immediately outside of the lymph trunks in the region just above the bifurcation of the aorta. Cephalad to this point the extravascular lymphocytes were progressively less in number, the least number being near the point of ligation of the thoracic duct in the chest. A heavy concentration of these cells was also observed around the intestinal trunks near their entrance into the

cisterna chyli. This region, incidentally, had the greatest number of lymphocytes in the 2 other animals in the series. In 1 of these 2 cats the lymphocytes were so heavily masked that they resembled a small lymph nodule (figs 1 and 2), even though the thoracic duct had been obstructed for only three hours. In another animal the concentration of lymphocytes on both sides of the wall of a lymph vessel was so great that a direct transition seemed to exist (figs 3 and 4). In the third animal the effect of a twenty-six hour obstruction of the thoracic duct on a lymph gland was shown (figs 5 and 6). Here the cortex was relatively compact when compared with the edematous medulla with its thin, delicate tissues separated and teased in a fashion which made for better histologic study. Possibly lymphatic obstruction might be used as a means for obtaining finer morphologic details not only of lymph glands but of other organs. The coronary lymph sinus of the lymph gland was small when compared with the extremely large collecting trunks at the hilus.

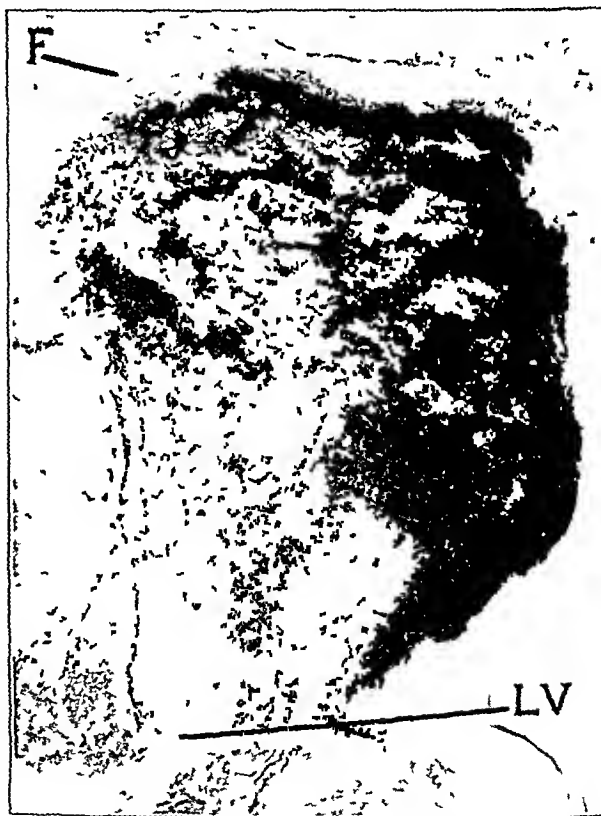


Fig 2—Enlargement of area L1 in figure 1, to show the irregular packing of lymphocytes outside of a lymph vessel. A few lymphocytes are enmeshed in a fibrin-like network, F. A lymph vessel is LV. Hematoxylin and eosin stain, $\times 70$.

Commonly the extensive collections of extravascular lymphocytes are enmeshed in a thin, delicate, lightly eosin-stained meshwork, which resembles fibrin in appearance but is probably

extravasated chyle. This belief is strengthened by the fact that the fluid substance in adjacent chyle-bearing lymph vessels has the same appearance.

Because of the heavy concentration of lymphocytes on each side of the thin wall of a lymph vessel, it was hoped that the actual passage of the lymphocytes through the vessel wall might be studied. Although the preparations were not convincing, the impression was gained from the study of those fields in which the wall of the lymph vessel was cut at a slight angle, so that the endothelial cells were visible as a small plaque, that the lymphocytes passed, if not between, at least through the periphery of, the endothelial cells.

Nor was there a parallelism between the concentration of extravascular lymphocytes and extravasated chyle, because it was common to find the lymphocytes in dense masses, which resembled ribbons, with no chyle present, and on the other hand there were areas with large amounts of chyle which contained only a few lymphocytes. It was not unusual to find small lymph vessels completely packed with lymphocytes, yet rarely was a large vessel more than one-half full of these cells (fig 3). The areas of heaviest condensation of lymphocytes were not necessarily within the lumens of the lymph vessels but preferably immediately outside of their walls (figs 2 and 4). Lymphocytes were commonly found on the outside of fat cells (fig 4) but never within them. Apparently, whatever the factors responsible for the transfer of lymphocytes from their intravascular to their extravascular position may have been—and intravascular pressure may well have been one of them—the effect of these factors was rapidly dissipated once the cells were outside of the walls of the lymph vessels, except for ribbon-like deposits and heavy concentrations (fig 2), which were not always near large lymph vessels but extended along thin fascial planes. Nor did the lymphocytes escape uniformly and evenly from the lymph vessels (fig 4).

It will be noted from the preceding description that the concentration of lymphocytes following ligation of the thoracic duct was in tissue essentially proximal to the intestinal lymph gland. What was happening to the lymphocytes in the mesenteric lymphatics immediately distal to the intestinal lymph gland was found from the histologic examination of sections taken from the same animal from which the material shown in figures 3, 4, 5 and 6 was taken and emphasizing the heavy concentration of lymphocytes within and without the lymph vessels. In marked contrast to this heavy deposition the lymphatics and the tissues just distal to the intestinal lymph

gland were entirely normal. The same results were obtained in another animal.

Since lymphocytes, which are of considerable size, can pass through lymph vessels, whose walls are many times thicker than a single endothelial layer, it does not seem unreasonable to believe that chyle can pass through this same type of wall, and probably more easily. The predication of a rupture of the wall is not necessary.

Furthermore, if chyle and lymphocytes can pass readily through the walls of lymph vessels, could also fine particulate matter under similar conditions? To get evidence for this possibility, commercial India ink, sold as Higgins Eternal Black Carbon Writing Ink, was injected centripetally, with the aid of a 10 cc syringe equipped

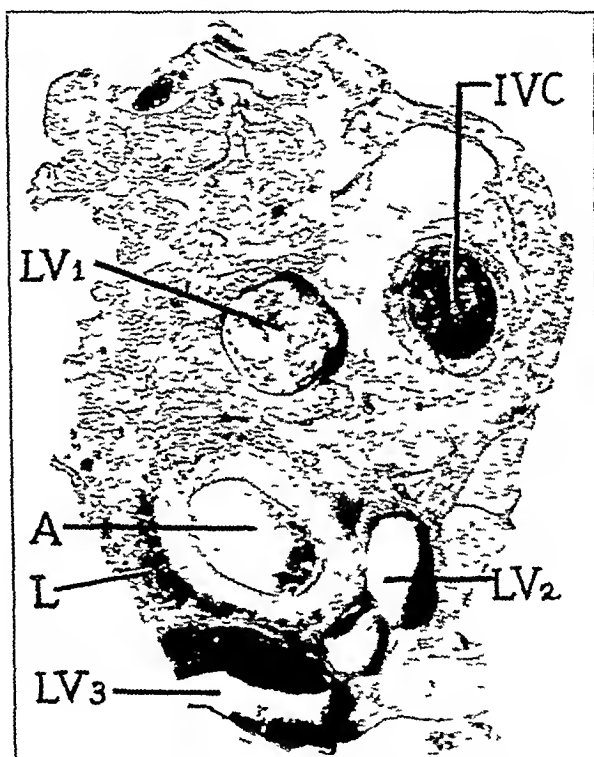


Fig 3—Cross section of the posterior abdominal wall of a cat whose thoracic duct had been ligated twenty-six hours before to show the concentration of lymphocytes (black) within the larger lymph vessels, *LV1*, *LV2* and *LV3*, and also at *L* in the adventitia of the aorta, *A*. *IVC*, inferior vena cava. The area *LV1* is shown enlarged in figure 4. Hematoxylin and eosin stain, $\times 13$.

with a 27 gage needle, into the mesenteric lymphatics of a cat anesthetized with ether. The ink went quickly to a mesenteric lymph gland, which soon became black, but in the meantime the mesenteric lymph vessel which had been receiving the injection no longer had its sharp outline but was becoming blurred, beadlike and fuzzy. As the injection was continued the lymph vessel became indistinct, until it resembled a concatenation of black smudges. Histologic examination of the lymph vessel showed that the

ink had gone through the wall of the vessel and had distributed itself in the surrounding, loose areolar tissue. There was no sign of rupture in the wall. This experiment was repeated in 6 animals. In 2 cases the mesentery with its fuzzy lymph vessels was cleared by the Spalteholz method. Examination of such a specimen showed that the particles of ink were in greater concentration immediately outside of the vessel and gradually became more scattered as the distance from the vessel increased. The heavy concentration was not uniform along the vessel but was in waves, more or less evenly spaced.

In fact, in 2 animals it was shown that a direct relationship existed between the amount of pressure of the injected ink and the speed with which the fuzzy outline of the vessels developed

and cellophane were tried as dialyzing membranes, to simplify and standardize the procedure the suggestion of Dr. Edgar Poth to use Patapar paper was followed. A sheet of this paper was shaped into the form of a bag, and 200 cc. of the commercial ink mentioned previously was put in it. The neck of the bag was tied with heavy thread, and the bag was allowed to float on the surface of a sodium chloride solution of 0.89 per cent concentration, which filled a brom jar of 1 gallon capacity. The thread around the neck of the bag was then secured to a cross arm, so that this part of the paper bag was prevented from sinking any lower. For seven consecutive days saline solution was allowed to enter slowly at the bottom of the jar by means of a rubber tube and then flow over the top at a rate of 8 gallons

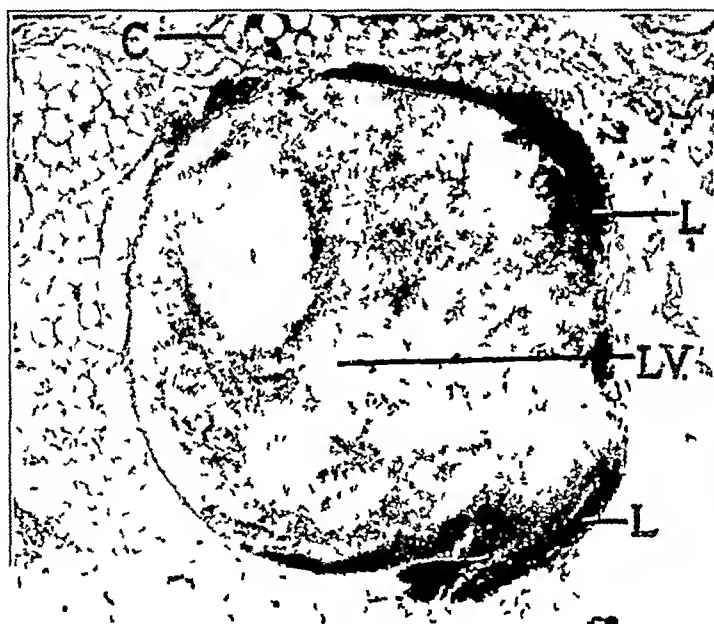


Fig. 4—Enlargement of area *LV 1* of figure 3 to show the unequal massing of lymphocytes *L1* and *L2* directly outside of a lymph vessel, *LV*. Opposite *C* the lymphocytes are concentrated on the periphery of fat cells but are never found inside these cells. Hematoxylin and eosin, $\times 50$.

Thus for a cat with pressures of 40, 40, 20, 110 and 160 mm. of mercury erected on the injection fluid, the corresponding periods for the appearance of the blurred outline of the vessels, a different lymphatic being used for each injection, were two and a half, three, five, two and three-fourths minutes respectively.

However, it was soon realized that no conclusions regarding the passage of ink particles through the walls of lymph vessels could be drawn from these experiments because the commercial ink had an ammoniacal odor. Hence the possibility arose that the ammonia may have damaged the walls and thus facilitated the passage of the ink particles.

To eliminate the ammonia factor the ink was dialyzed. After various thicknesses of celloidin

(30 liters) per day. In addition, the jar was completely emptied and freshly filled during the first five days. At the end of the week the ink within the paper bag was measured, and the average of three preparations was 230 cc. This showed that the ink had been moderately diluted by the saline solution. The dialyzed ink was kept in a glass-stoppered bottle and served as stock solution.

To test the toxicity of the dialyzed ink it was slowly injected by means of a syringe into the femoral vein of a cat, which was under light ether anesthesia. Into 1 animal 8 cc. was injected without any apparent harmful results, into another animal 20 cc. was injected, also without causing any ill effects. However, into a third cat 37.5 cc. was injected, this animal seemed well

for one hour later but was found dead the next morning. In none of the 132 experiments covered by this report did any animal receive more than 10 cc of the dialyzed ink. All reference to ink in the remainder of this article is to the dialyzed ink and not to the stock commercial ink. Furthermore, since the dialyzed ink had about the same specific gravity as the saline solution and since within the limits of the experiment differences between hydrostatic pressures of water and isotonic solution of sodium chloride could not be determined, for the rest of the report such pressures will be given in centimeter columns of water, even though ink was the actual measuring fluid.

Experiments were then undertaken to determine whether the ink particles would leave the lymph vessels the same way that the chyle and the lymphocytes did. In 6 cats the thoracic duct was ligated in the chest with the animal under intratracheal ether or pentobarbital sodium anesthesia, and then after respectively one, one, one and one-third, four, seventeen, and twenty-six hours the mesenteric lymph vessels were injected with ink by means of a 27 gage needle under a hydrostatic injection pressure which varied between 55 and 97 cm of water. The amount of ink injected varied between 2.6 and 3.2 cc. The injection apparatus was simple and consisted of the barrel of a 10 cc syringe, acting as a reservoir, to which was attached a rubber tube 3 feet (0.9 meter) long leading to the barrel of a tuberculin syringe, which in turn was equipped with the 27 gage needle. In all cases the ink was found in the same retroperitoneal regions as described previously for the chyle. The ink had a blue color, which increased in depth near the cisterna chyli, thus indicating the probable source of escape.

However, it still remained to be demonstrated whether the ink might not have escaped through a small rupture of a lymph vessel near the cisterna chyli, instead of having permeated the wall of a lymph vessel. To throw light on this point, the trunks of 3 animals described in the preceding paragraph were fixed in solution of formaldehyde, and later the pertinent structures, extending from and including the point of ligation of the thoracic duct in the chest down to the iliac vessels and including the entire lymphatic system from the intestine to the thoracic duct, were removed in one piece and cleared by the Spalteholz method. Subsequently this entire block of tissue was cut transversely with a safety razor blade into thin slices, which were from 2 to 3 mm thick. These thin preparations were then examined for places where the ink might have left a lymph vessel because of a rupture in the wall. None was found.

Objection might be raised to the high injection pressure of the ink, which was 97 cm of water in 1 case, so far as this pressure might be relatively excessive and thus simply force the inert particles through the wall of a lymph vessel whose exit was blocked mechanically by a ligation. To meet this criticism ink was first injected into the mesenteric lymph vessels of 3 cats in which there was no obstruction to the thoracic duct. Then the duct was tied, and in all 3 experiments the ink again found its way out of the lymph vessels chiefly at the cisterna chyli. One of these specimens was cleared by the Spalteholz method and examined as described before, and here also no rupture of a lymph ves-

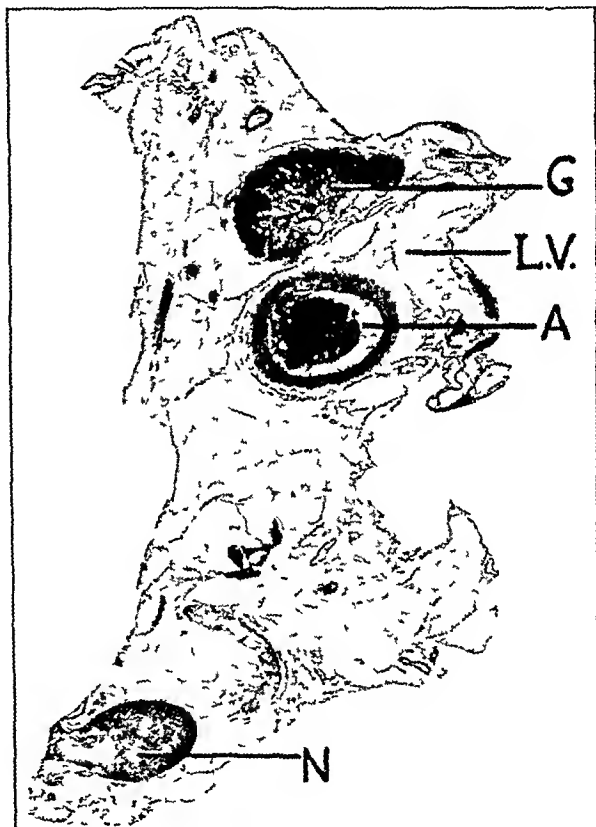


Fig 5—Cross section from the same animal as figure 3, to show the relative size and position of the lymph gland, *G*, with reference to the large lymph vessel, *L.V.*, and the aorta, *A*. A sympathetic nerve ganglion is at *N*. The gland, *G*, is enlarged in figure 6. Hematoxylin and eosin, $\times 6$.

sel to account for the extravasated ink was observed.

If intralymphatic pressure was responsible for the passage of the ink particles, as just mentioned, that pressure must have developed within the peripheral lymph system itself and not from any extraneous source, such as an injection fluid.

In observing a mesenteric lymphatic during its injection with ink under a pressure of 90 cm of water, it was seen that the vessel first showed

a slight, generalized, uniform enlargement which extended to the intestinal lymph gland. As the injection was continued, the vessel became still larger but revealed points of constriction about 2 to 3 mm apart, which gave the lymphatic a beaded appearance. The next change, which never occurred until two minutes, and frequently five minutes, after the injection had been started, was the beginning of a blurred outline of the lymph vessel. It was common for this fuzzy appearance to begin in the region of the intestinal lymph gland and not at the point of the injection. If the injection was continued for periods much over five minutes, then the entire perivascular region was covered by a series of ink splashes, which destroyed all markings.

This fraction was expected to contain the large particles of ink. Measurements of these small and large particles were made with the aid of an oil immersion lens and a micrometer eyepiece, and it was found that the small particles varied up to 1 micron in size, whereas the large particles ranged from 12 to 3 microns. Although the dividing band between these two groups was not broad, 4 experiments were carried out to determine whether any difference in their penetration of walls of lymph vessels could be observed.

The first animal had its thoracic duct tied twenty-six hours before, and when the large particles of ink were injected into the mesenteric lymphatics it was found that even with an injection pressure of 70 cm of water the ink did

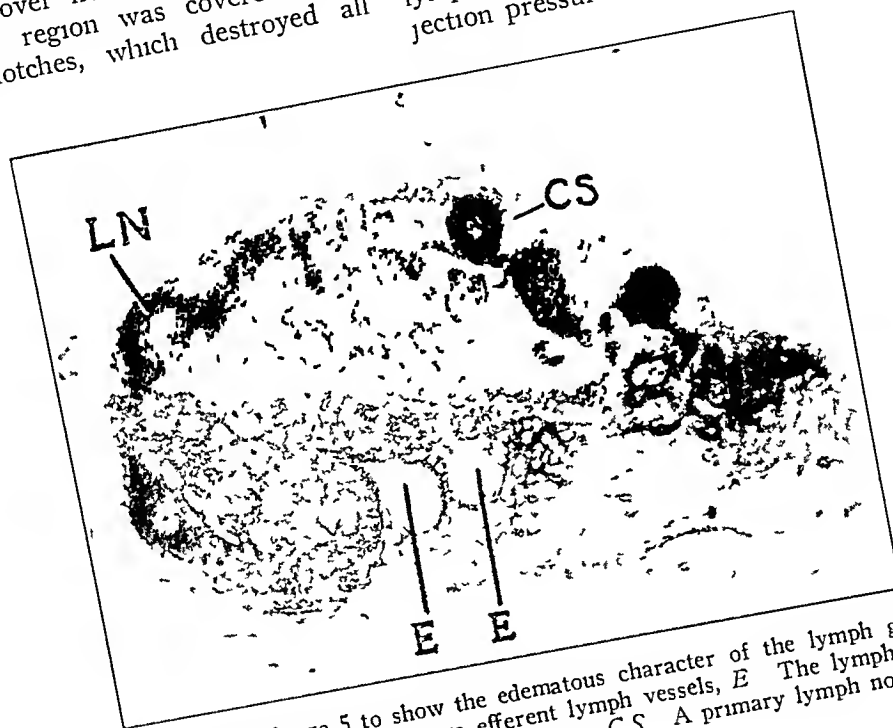


Fig 6—Enlargement of G in figure 5 to show the edematous character of the lymph gland twenty-six hours after ligation of the thoracic duct. Note the large efferent lymph vessels, E. The lymph vessels in the medulla are much larger than those in the cortex or the cortical sinus, CS. A primary lymph node is at LN. Hema-toxylin and eosin, $\times 30$.

Again, it might be said that the ink particles, being extremely small, might not require much pressure to force them through the wall of a lymph vessel. To obtain information on the size of the ink particles and their corresponding ability to go through a lymphatic wall, some of the ink was centrifuged at 2,200 revolutions per minute for two hours and forty minutes. At the end of this time the specimen looked uniformly black, and from the top of each centrifuge tube 15 cc of ink was carefully aspirated with the aid of a needle and a syringe. This fraction was supposed to have the smallest particles. The ink remaining in the centrifuge tube was decanted and at the bottom of the tube was found a small black deposit, which was shaken up in a small amount of saline solution

not pass through the walls of the lymph vessels while the injection was continued respectively for three and five minutes. However, when the injection of one vessel was maintained constantly for seventeen minutes not only did the vessel become large like the other two but a slight blurring of its wall was noted. It is possible that the smaller particles were thus able finally to permeate and go slightly beyond the wall of the lymph vessel.

In the second animal, under the same general conditions, with a pressure again of 70 cm of water, four injections were made for an interval of three, eight, eight and ten minutes respectively. No blurred outline of lymph vessels was observed. In the third animal, under the same general conditions, it was finally possible to inject one

lymph vessel continuously for ten minutes, no fuzziness occurred

The last animal in this series was prepared like the previous 3. The injection pressure was, as before, 70 cm of water. First the large particles were injected into a lymph vessel for five minutes, then the injection apparatus was drained, washed out and filled with ink having the small particles. Two injections of five and eight minutes respectively were made. Then the apparatus was drained, washed out and filled with the ink containing large particles. A single injection for eight minutes was made. Thus the injections of the small particles were flanked by the injections of the large particles. No fuzziness was observed in the outline of any of the vessels. The entire preparation was cleared by the Spalteholz method, and when examined under the Greenough binocular microscope it was seen that fine particles of ink were outside along the course of the lymph vessels which had received the small particles but only within a range of about 2 cm from the mesenteric lymph gland, no ink particles were seen outside of the vessels filled with the large particles. In these 4 animals pentobarbital sodium was the anesthetic. It was chosen in order to obviate a possible objection to a dilatation which ether as the anesthetic might have given.

It seemed, then, that the size of the particle made a difference in the penetration, and to add to this concept 1 animal, whose thoracic duct was ligated twenty-three hours before, received an injection of a 3 per cent aqueous solution of trypan blue, which consists of particles finer than those of india ink. The injection was made into the mesenteric lymph vessels with syringe and needle without a record of pressure. It was seen at once that the dye diffused through the wall of a lymph vessel twice as quickly as the ink. In another cat the same experiment was repeated except that the injection pressure was 70 cm of the dye to correspond to the injection pressures used in the experiments mentioned previously. In this case the dye passed through the vessel wall within eight seconds.

In view of the relatively high injection pressures—about 70 cm of water—the possibility existed that the injection pressure alone might be responsible for the passage of the ink particles through the walls of the lymph vessels in the region of the cisterna chyli following ligation of the thoracic duct, even though the mesenteric lymph gland interposed. Accordingly, it seemed reasonable first to inject the mesenteric lymphatics. Since presumably no obstruction of the lymph vessels existed, the ink would flow into the veins at the termination of the thoracic

duct in the base of the neck without any trouble, and the injection pressure would be of little moment. Then the thoracic duct in the chest was to be tied. From this time on the pressure in the inferior part of the thoracic duct would build up of itself, and if any ink escaped from the lymph vessels it would be due to this pressure and not to the initial injection pressure. In the first animal, under pentobarbital sodium anesthesia, 8 cc of the ink was injected into the mesenteric lymphatics with syringe and needle in twenty minutes. The abdomen was closed, and the thoracic duct was ligated in the chest. Thirty-five minutes later the abdomen was again opened, and a bluish discoloration, obviously ink, was found in the left renal region. The whole trunk was fixed in 4 per cent solution of formaldehyde, and histologic sections taken through the cisterna chyli showed that ink was outside of the lymph vessels.

In the second animal, 2.5 cc of ink was injected into the mesenteric lymphatics in seventeen minutes at a fixed pressure of 70 cm of water. The thoracic duct was ligated nine minutes later, and the region of the cisterna chyli on the left side was observed thirty minutes subsequently, when a questionable faint bluish discoloration was noted. However, twenty minutes later the color was definitely blue, and fifteen minutes later the color was still deeper. Examination of the cleared specimen showed the ink distributed in the loose areolar tissue about the cisterna chyli. There was no rupture of the lymph vessels.

Since the experiments were leading into the field of lymph pressures, it seemed of interest to determine what some of the intravascular lymph pressures were. On gross inspection, when a cat's mesenteric lymph vessel was opened with a needle or sectioned with a quick snip of the scissors, the lymph rolled out limpidly and gave no evidence of spurting as if under pressure. The pressure, then, in these vessels must be low. To measure it, the same simple apparatus as described before was used. The mesenteric lymphatics were filled with ink, the barrel of the 10 cc syringe, serving as a reservoir, was attached to an arm which could be moved up and down on a stand, so that different pressures of ink could be obtained.

To measure the pressure in the mesenteric lymphatics with this apparatus, the level of the ink in the reservoir was placed about 3 cm above the level of the vessel into which the injection was to be made. At this low pressure ink would roll out of the needle slowly, but when the point of the needle was bathed in the warm saline solution with which the assistant constantly

irrigated the preparation the ink would flow more freely and would obscure the lymph vessel to be injected were it not for this frequent washing. Once the point of the needle had entered the lymph vessel, the ink particles could be seen on the bevel of the needle, and as the reservoir was raised a level was reached at which the ink would leave the point of the needle and slowly continue its flow into the lymph stream. At this moment, with the aid of calipers, the height of the level of the ink in the reservoir above the point of the needle was measured. This measurement was considered to be the pressure within the mesenteric lymph vessel, and from a series of 8 animals the pressure was found to be respectively 3.0, 4.0, 5.3, 5.3, 5.9, 6.0, 6.7 and 6.8 cm of water, the average being 5.2 cm of water.

In animals with a large amount of fat in the mesentery, not only was it difficult to enter a lymph vessel but because a certain depth of fat had to be pierced to reach it the point of the needle was frequently blocked and higher readings were obtained. Lean animals always gave better preparations.

The preceding figures represent the end pressure within the mesenteric lymph vessel proximal to the site where the point of the needle came to rest when it was directed, as always toward the intestinal lymph gland. Because the shaft of the needle near its point completely filled the distal segment of the lymph vessel and thus prevented lymph from passing along the outside of the needle, these figures do not represent side pressures. It is doubtful whether there is much difference between the side pressure and the end pressure as determined by the method just described. Possibly the figures given are a little low since the direction of the flow of lymph is away from the point of the needle, however, the amount and the rate of flow must of necessity be very small. Any one having access to the fine glass capillary needles used to determine intracapillary blood pressure could easily determine the side pressure in the mesenteric lymph vessels. Apparently this type of equipment was used by Königges and Otto⁴ in 1937 when they found that the pressure within the lymphatic of an intestinal villus of a cat anesthetized with dial was 33.3 cm of water. The steep gradient of this figure to 5.2 cm of water, which is the average of the values obtained for the mesenteric lymph pressures, is striking.

4 Königges, H. G. and Otto, M. Studies on the Filtration Mechanism of the Intestinal Lymph and on the Action of Acetylcholine on It and on the Circulation of the Intestinal Villi. *Quart J Exper Physiol* 26: 319, 1937.

It is not the purpose of this paper to explain this difference or to enter into a discussion of the forces responsible for the production of lymph. Enough evidence has not accumulated to make such a correlation possible. However, according to Königges and Otto the hydrostatic pressure within the central lymphatic of a villus of the small intestine of a cat is 33.3 cm of water, and the capillary blood pressure in a neighboring villus is 42.6 cm of water. What apparently is not known is the tissue pressure for the villus. The nearest approximation, probably, to this value is that for the subcutaneous tissue of man as obtained by Wells, Youmans and Miller,⁵ and it is about 7 cm of water.

Objection may properly be made to the use of this figure for tissue pressure in the villus, and yet, even though there is some fundamental histologic similarity in the two areas, the tissue pressure in the villus could be 21 cm of water and still not invalidate the conclusion that obviously lymph is not going to collect in a lymph capillary when the hydrostatic pressure within that capillary is 33.3 cm of water and the pressure in the surrounding tissue is only 7 or even 21 cm of water. Osmotic pressure must make up the difference. To obtain this osmotic pressure, proteins must be present in the lymph capillary in a higher concentration than in the fluid of adjacent tissue. But Drinker and Yoffey⁶ stated that lymph and tissue fluid are approximately identical, therefore, there can be no material difference in the osmotic pressure of these two fluids. If Königges and Otto are correct, then there must be a high concentration of proteins in the lymph capillaries, with a gradual reduction as the lymph reaches central and larger lymph vessels, from which collection of the fluid is simple and for which chemical analyses have shown that the protein content is relatively low (Drinker and Yoffey). That there might be such a difference in protein content for various lymph vessels is a new physiologic concept for this vascular system. On the other hand, if subsequent work supports that of Drinker and his associates, the figure of 33.3 cm of water for the hydrostatic pressure in a lymph capillary as determined by Königges and Otto is too high. But since these two authors used the same technic for measuring pressures in capillaries as they did for determinations on blood capillaries and obtained values for the pressure in blood capillaries which

5 Wells, H. S., Youmans, J. B., and Miller, D. G., Jr. Tissue Pressure (Intracutaneous, Subcutaneous and Intramuscular) as Related to Venous Pressure, Capillary Filtration, and Other Factors, *J Clin Investigation* 17: 489, 1938.

6 Drinker, C. K. and Yoffey, J. M. *Lymphatics, Lymph and Lymphoid Tissue*, Cambridge, Mass., Harvard University Press, 1941.

agree in general with those of other investigators one naturally turns reluctantly to the technical method as a source of error, particularly since this method has been widely adopted. Before any conclusions can be drawn, three determinations are required: first, of the tissue pressure in the villus, second, of the protein content of the central lymph capillary of the villus, and, third, of the protein content of the fluid giving rise to the tissue pressure. For the present it would seem that the value of the pressure in a lymph capillary as determined by Koniges and Otto is too high.

To return to the consideration of the gradient of the pressure from 33.3 cm of water in the central lymph capillary of the villus to 5.2 cm of water in the mesenteric lymphatic, it is possible but not probable that an extremely small lymph gland or even lymph follicles intercalated between these two areas might account for the extensive difference. But that a large lymph gland, such as the intestinal lymph gland at the root of the mesentery in a cat, might act as a pressure buffer was shown by the following experiments.

The problem was to find out whether ligation of the thoracic duct in the chest would cause sufficient back pressure to increase the pressure in a mesenteric lymph vessel.

In the first cat, the pressure in the mesenteric lymph vessels was measured one and two-thirds hours after ligation of the thoracic duct. The pressure in six successive lymphatics was 3.2 cm of water. In the second animal, under ether anesthesia also but two and two-thirds hours after ligation, the pressure was 5.8 cm of water. The third animal, four and one-sixth hours after ligation, showed a pressure of 3.2 cm of water in each of six different vessels. For the 3 remaining animals of this series, the interval between the ligation and the taking of pressure was respectively twenty-five and three-fourths, twenty-six and twenty and one-half hours, the corresponding pressures were 6.0, 5.5 and 5.7 cm of water. It is thus apparent that ligation of the thoracic duct had little effect on the pressure of a mesenteric lymph vessel particularly when compared with an average of 5.2 cm of water in animals mentioned previously who had had no previous ligation of the thoracic duct.

But the relationships between the pressure at the point of ligation of the thoracic duct and that in the intestinal lymph gland still were unknown. Previous work in 1923,⁷ had shown that lymph pressure was gradually built up be-

hind the thoracic duct when it was obstructed in the base of the neck. That this pressure might be considerable even in the intestinal lymph trunks was accidentally discovered in a cat whose thoracic duct had been ligated an hour and a half before. A snip with scissors of an intestinal trunk sent up a sudden spurt of lymph to a height which was estimated to be about 15 cm. That such a pressure was present in what seemed to be only a moderately distended lymph vessel was not suspected.

To determine what the ordinary pressure in the mesenteric lymph vessels was as compared with that in the intestinal trunks, for 3 animals under pentobarbital sodium anesthesia the following respective values expressed in centimeters of water were obtained: 3.0 and 0.5, 5.3 and 1.3, 6.7 and 1.0. Obviously, the intestinal lymph gland acted as a pressure buffer. In this respect one can only speculate that the normal function of a lymph gland is to prevent a sudden flood of lymph from passing suddenly into a reservoir, like the cisterna chyli. These receptacles may be unable to pass the lymph along as fast as it is received, and thus build up pressure and force the lymph to permeate the walls of the lymph vessels and to collect in the perivascular spaces and, by implication also, in the peritoneum or other mesothelial-lined spaces. With the lymph gland standing as a guard under normal conditions, adjustments of volume and pressure of the lymph may be established in the periphery. Even in disease, such as inflammation, the lymph gland may be able to adjust much greater degrees of lymph pressure and volume.

However, with the thoracic duct tied in the chest, the pressure relationships were opposite to those given in the preceding paragraph. In 4 cats in which the duct had been tied respectively two and two-thirds, four, twenty-six, and twenty-six and one-half hours before, the corresponding pressures of a mesenteric lymph vessel and an intestinal lymph trunk were respectively 5.8 and 21.1, 3.2 and 16.5, 5.5 and 30.0, 5.7 and 63.5 cm of water.

These measurements showed that ligation of the thoracic duct did not increase the pressure in the mesenteric lymph vessels but did raise the pressure in the intestinal trunks. It should be noted that in the last 3 of the 4 animals just mentioned the pressure within the intestinal lymph trunks was measured by inserting an 18 gage needle attached to a glass tube having a millimeter bore. The height to which the lymph rose in the tube was considered to indicate the lymph pressure of the side wall since the needle did not obturate the lumen of the vessel, the walls of the intestinal lymph

⁷ Lee, F. C. Some Observations on Lymph Pressure. *Am. J. Physiol.* 67:498, 1923-1924.

thin and since even slight manipulation of the needle would enlarge the opening of the wall to a greater size than that obstructed by the needle, thus causing a leak and producing a low pressure reading, the shaft of the needle near the point was coated heavily with petrolatum in order to seal the leak around the needle.

That such a high lymph pressure as 63.5 cm of water could be developed is not surprising in view of the pressure of 120 cm which Field, Drinker and White⁸ obtained in the leg of a dog above the site of a sterile inflammation. In all probability the valves in the lymph vessels, in addition to the structure of the intestinal lymph gland, were responsible for the gradient of pressure, which was normal in the mesenteric lymph vessels. Of these two factors, it is believed that the lymph gland played the larger role, because both pressure readings were taken near the gland, which eliminated the consideration of many valves. Besides, the edematous character of the medulla of the lymph gland, as shown in figure 6, indicated that the valves in the efferent vessels were not competent.

The fact that the intestinal lymph gland acted as a barrier between the high pressures built up in the intestinal trunks and the low pressures in the mesenteric lymphatics following ligation of a thoracic duct may indicate that the pressure was probably the chief factor responsible for the extravasation of lymphocytes, as mentioned earlier in this report.

It may be well to point out that since small particles may pass through the wall of a lymph vessel, particularly when the pressure within the vessel is high, the condition of lymphangitis may be due to an inflammatory reaction around bacteria situated within the wall of the lymph vessel or immediately outside of it.

Again, since certain portions of a lymph vessel such as the segment immediately distal to the intestinal lymph gland, seem to be more permeable than other sections, it is possible that such a weakness may be responsible for the formation of lymph cysts.⁹

There still remained the consideration of whether the intestinal lymph gland would act as a buffer should the pressure in the mesenteric lymph glands be raised. Ordinarily it might be expected that the lymph node would not impede an excessive flow of lymph which is moving in its normal channels and in the normal direction. And if the volume of lymph were increased, would the proximal portion of the lymph gland

allow it to pass as fast as it was presented or would the lymph stream be impeded and pressure built up on the distal side of the gland?

To throw some light on this problem, an increased flow of lymph from the small intestine was obtained by injecting 0.2 cc of turpentine with a 27 gage needle into the antimesenteric serosa every inch (2.5 cm) for 10 inches (25 cm) of a cat's small intestine in the direction of normal peristalsis after the pressure of a control mesenteric lymph vessel just proximal to the injected segment had been taken. Pressure readings were then observed in the successive mesenteric lymphatics which drained the segment of the bowel which had been treated with turpentine. In the first animal, this pressure increased from 6.6 cm to 40.5 cm of water by the end of seventeen minutes, successive distal vessels for each determination being used. After five more minutes, the same reading of 40.5 cm was obtained. By this time the mesenteric lymph vessels were larger and fuller, indicating an increase in the amount of lymph. At this point the pressure of an intestinal trunk was measured. The reading was 11.5 cm of water, indicating a distinct difference in pressure between the two sides of the lymph gland.

The second cat was pregnant, weighed 4 Kg and showed a gradual rise of pressure in a mesenteric lymph vessel from 5.9 cm to 23.7 cm of water by the end of one and one-third hours. Fourteen minutes after this highest reading had been taken, the pressure had fallen to 13.6 cm of water. At this point the lymph pressure in an intestinal trunk was 4.1 cm of water.

In the third animal, the pressure in a mesenteric lymph vessel increased from 6.0 cm to 23.6 cm of water at the end of fifty-seven minutes, at which time, with the pressure still going up, the pressure of an intestinal lymph trunk was 14.6 cm of water.

The observations on 3 animals showed that the intestinal lymph gland would buffer volumes and pressures of lymph flowing in the normal direction, but not as effectively as when it was flowing in the reverse direction. Probably the valves of the lymph vessels might account for some of this difference. In addition, small amounts of turpentine possibly were carried along in the lymph stream and reached the lymph gland, causing enough irritation to produce, even in such a relatively short time, some obstruction to the lymph channels, which accounted for a difference in pressure.

That the lymph gland, in view of the pressure relations just described, is in any way comparable

⁸ Field, M. E., Drinker, C. K., and White, J. C. Lymph Pressure in Sterile Inflammation, *Exper Med* 56:363, 1932.

⁹ Lee, F. C. Large Retroperitoneal Chylous Cyst, *Arch Surg* 44:61 (Jan) 1942.

to the possible buffer action of the blood vessel rete mirabile, which cushions the central nervous system of whales (cetacea), is purely speculative.

A few general remarks about the experiments may now be made.

At first the anesthetic used was intratracheally administered ether. But when the possibility arose that this anesthetic might be partly responsible for the permeability of lymph vessels, pentobarbital sodium was employed intraperitoneally, in a dose of 0.7 cc of a 5 per cent aqueous solution per kilogram of body weight. Even the thoracic duct in the chest was ligated with the animal under general pentobarbital anesthesia. However, it was soon felt that there was little difference in the action of the two anesthetics as far as these experiments were concerned, and the majority of the animals received pentobarbital, ether being given only when the thoracic duct was ligated in the chest. No experiments were made to determine whether the pentobarbital sodium administered intraperitoneally had any direct effect on the lymph vessels.

Great help was derived from the use of a small loupe, which was worn like a pair of spectacles and which gave a magnification of about three diameters. It was used for every injection.

The animals were kept warm by means of an electric light, which was placed near the structure under examination. Frequent washing with warm saline solution prevented drying of the tissues.

Whenever it was desired to have the mesenteric lymphatic system filled with chyle, the cat was starved for twenty-four hours and then fed rich milk at least three, preferably four, hours before the anesthetic was given. Meat as a substitute for the milk was unsatisfactory because it increased the time required for the formation of chyle.

SUMMARY

In experiments on cats it was found that ligation of the thoracic duct in the chest produced an extravasation of chyle, first in the region of the cisterna chyli, as early as forty-five minutes

after the operation. From this general region the chyle spread retroperitoneally and also into the leaves of the mesentery. Small lymph glands became edematous.

Under these conditions, the lymphocytes were concentrated in the lymph vessels distal to the ligation of the thoracic duct but not beyond the intestinal lymph gland, which acted as a barrier. In addition, a large number of lymphocytes passed through the walls of the lymph vessels and were frequently deposited in masses resembling lymph glands. The greatest concentration of the lymphocytes was in the region immediately below the renal veins. It is probable that intralymphatic pressure played a part in forcing the lymphocytes into this extravascular position.

Commercial india ink when injected into the mesenteric lymphatics soon passed through the walls of these vessels without causing a rupture. When this ink was used after having been dialyzed against saline solution, permeation did not occur so readily.

When the thoracic duct was ligated first, the dialyzed ink passed through the lymph vessels like chyle and lymphocytes, without requiring a rupture of the walls.

It was found that the large particles of centrifuged, dialyzed ink were held back by the walls of the lymph vessels, whereas the small particles passed through. Trypan blue, containing still smaller particles, went through more readily.

Pressure within the mesenteric lymph vessels was found to be about 5.2 cm of water, in the intestinal lymph trunks, about 1.0 cm of water.

Ligation of the thoracic duct in the chest caused no appreciable increase in the pressure in the mesenteric lymph vessels, but it did cause the pressure in the intestinal lymph trunks to rise to as much as 63.5 cm in 1 instance. The large intestinal lymph gland seemed to act as a buffer in the lymphatic system.

This gland also acted as a buffer when the pressure in the mesenteric lymph vessels went as high as 40.5 cm of water while that in the intestinal trunks registered only 11.5 cm.

ADMINISTRATION OF SUCCINYLSULFATHIAZOLE BEFORE AND AFTER HEMORRHOIDECTOMY

LIEUTENANT LEO L LEVERIDGE

MEDICAL CORPS, ARMY OF THE UNITED STATES

Hemorrhoidectomy is an elective operative procedure, traditionally performed in a contaminated field. The presence of large numbers of potentially pathogenic bacteria in this operative site, and flowing over the healing wounds post-operatively, has always had to be accepted as unavoidable. With recent developments of chemotherapy, means appear now within reach to alter these conditions.

Two drugs, sulfanilylguanidine and succinylsulfathiazole,¹ have been reported to decrease the bacterial flora in the gastrointestinal tract, apparently without excessive systemic absorption. The newer drug, succinylsulfathiazole,² appears to be less toxic and yet to be as effective as sulfanilylguanidine with the additional advantage of being effective in the presence of ulcerating lesions of the bowel.³

This study was made possible by the cooperation of the following officers of the Medical Corps of the Army of the United States on the staff of the Station Hospital Camp Blanding, Fla: Major J V Freeman, Chief of the Surgical Service, Major J E Ryan, Chief of Septic Surgery, and Major J T Cuttino, Chief of the Laboratory Service. The problem was suggested by Major J W Annis, Chief of the Gastrointestinal Section of the Medical Service, and the work could not have been done without the assistance of Major A Fodor, Sanitary Corps, Army of the United States, Assistant to the Chief of the Laboratory Service.

Dr E J Poth, Galveston Tex., and Dr E L Burbidge, Sharp and Dohme Philadelphia, made many helpful suggestions.

1 The succinylsulfathiazole (sulfasuxidine) employed in this study was furnished by Sharp & Dohme, Philadelphia.

2 Miller, E., Rock, H J., and Moore, M L. Substituted Sulfanilamides. N⁴-Acyl Derivatives, *J Am Chem Soc* **61** 1198 1939. Moore, M L. and Miller, C S. Dicarboxylic Acid Derivatives of Sulfanilamides. *ibid* **64** 1572 1942.

CHEMISTRY OF SUCCINYLSULFATHIAZOLE

Structurally, succinylsulfathiazole is a succinic acid derivative of sulfathiazole. It is relatively strongly acid in reaction. Its solubility in water is low, 0.070 Gm dissolving in 100 cc of water at 37 C. However, the sodium salt of succinylsulfathiazole is considerably more soluble, as much as 50 Gm can be dissolved in 100 cc of water.

TOXIC REACTIONS TO SUCCINYLSULFATHIAZOLE

Toxic manifestations of succinylsulfathiazole reportedly are "infrequent and mild. An occasional individual may complain of dizziness, headache, or loss of appetite."⁴ There have been recorded, however, 2 instances of severe reaction. In 1, which was the only instance of such reaction among a total of 250 patients receiving the drug, the patient had a prompt recovery,⁴ in the other, an isolated case, the patient succumbed to a fatal agranulocytosis.⁵ Both patients were noted to have headache, nausea and vomiting, and chills and fever. Each of the 2 manifested a reaction to plain sulfathiazole as well as to the succinylsulfathiazole. It may be postulated that these patients were hypersensitive to sulfathiazole, which is reported to be liberated from succinylsulfathiazole by hydrolysis in the intestines and the liver.³

3 (a) Poth, E J., Knotts, F L., Lee, J T., and Inui, F. Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives. I. Succinylsulfathiazole, a New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, *Arch Surg* **44** 187 (Feb) 1942. (b) Poth, E J., and Knotts, F L. Clinical Use of Succinylsulfathiazole, *ibid* **44** 208 (Feb) 1942.

4 Poth, E J. Succinylsulfathiazole. An Adjuvant in Surgery of the Large Bowel, *J A M A* **120** 265 (Sept 26) 1942.

5 Johnson, S A M. Acute Agranulocytosis Due to the Administration of Succinylsulfathiazole, *J A M A* **122** 668 (July 3) 1943.

BACTERIOLOGIC STUDIES OF SUCCINYL-SULFATHIAZOLE

E J Poth and his associates have made the original basic study of succinylsulfathiazole.³ They have shown the drug to be almost totally lacking in antibacterial activity in vitro against *Escherichia coli* but in vivo to decrease the coliform bacteria count from about 10,000,000 to less than 1,000 organisms per gram of wet stool in one to seven days (usually in three to five days) of oral administration.

In addition to *Esch coli*, they observed that the Shiga, Flexner and Sonne strains of the dysentery bacillus were especially susceptible to the antibacterial action of this compound. The specific action of succinylsulfathiazole on the dysentery bacillus (Flexner) has been confirmed.⁶ Apparently other organisms in the intestines were affected by succinylsulfathiazole given orally, although these were not identified.

It was reported⁴ that the gram-positive and the gram-negative organisms, which are normally equal in number, decreased under succinylsulfathiazole therapy at approximately the same logarithmic rate for a few days, until the gram-positive population became constant. The number of gram-negative bacteria continued to fall and this decrease was said to be due not solely to the change in coliform organisms.

The drug was said to have no apparent effect on the growth of the typhoid and paratyphoid organisms, *Streptococcus faecalis alpha* or *Bacillus proteus*. Also, *Aerobacter aerogenes* was considered more resistant than *Esch coli* to the action of succinylsulfathiazole.^{3b}

With succinylsulfathiazole therapy the stools became soft, gelatinous, mucoid, paler and relatively odorless, contained visible undigested food particles and were smaller in bulk.

REPORTED APPLICATIONS OF SUCCINYL-SULFATHIAZOLE IN SURGICAL PRACTICE

It was reported that at laparotomy following preoperative preparation with succinylsulfathiazole the bowel was found to be collapsed and free from gas and fecal material. The mucosa showed no evidence of local irritation due to

action of the drug. In an experiment, the colon of a dog receiving this therapy was divided transversely through one third of its diameter, and the lesion was observed to heal without the production of fatal peritonitis, provided that the bowel was found empty at the time of laparotomy.^{3b}

A series of 50 patients undergoing surgical treatment of the large bowel who were given the drug as preoperative preparation and as postoperative therapy were observed to have an unusually smooth postoperative course. Serious complications due to infection following fecal contamination were not encountered, and shortened periods of hospitalization and of convalescence were reported.⁴

PRESENT STUDY

It was decided to study a small, controlled series of patients subjected to hemorrhoidectomy to whom succinylsulfathiazole was given preoperatively and postoperatively in order to determine whether this drug promised to alter the usual postoperative course.

All patients with uncomplicated hemorrhoids admitted to the station hospital, Camp Blanding, Fla., for surgical treatment during a seven week period were included in this study. As the patients were admitted, all but 1 were alternately placed in the group receiving succinylsulfathiazole or in the control group. Cooperation was voluntary on the part of the soldiers, and only 1 patient declined to take the drug. He was placed in the control group. Twenty patients were followed—10 controls and 10 receiving the drug. The average age of the men in each group was found to be 26 years.

Succinylsulfathiazole was given on the basis of 0.5 Gm per kilogram of body weight for the first twenty-four hours, followed by a maintenance dose of 0.25 Gm per kilogram daily, divided into six portions, to be taken every four hours. This was administered between five and nine days preoperatively, the average period being six and six-tenths days, and for twelve to fourteen days postoperatively. A smaller dose (0.1 Gm per kilogram daily) may be equally effective for maintenance after the coliform bacillus count of the stools has decreased to 1,000 organisms per gram or lower.⁷ It was felt however, that until the smaller dose has been generally accepted, in this new use of succinylsulfathiazole it was wiser to give the drug in amounts which had already been established as effective.

Patients receiving succinylsulfathiazole had complete blood counts and a urinalysis every other day. Levels of the sulfonamide drug in the blood were determined daily for the first few days and then about every third day. Coliform bacteria counts of the stools were fol-

6 Smyth, C I, Finkelstein, M B, Gould, S E, Koppr, T M, and Leeder, F S. Acute Bacillary Dysentery (Flexner). Treatment with Sulfaguanidine and Succinyl-sulfathiazole. J A M A **121** 1325 (April 24) 1943.

7 Burbidge, E L, Sharp & Dohme Medical Research Division. Personal communication to the author.

lowed For comparison, two or three complete blood counts were taken for each of the control patients

The controls were prepared with magnesium sulfate administered orally and a cleansing enema the night before operation, whereas both of these were omitted in the preparation of patients receiving succinylsulfathiazole (These patients at no time were given any laxatives, enemas or liquid petrolatum, which are said to impede the action of the drug³) At operation, feces were rarely encountered in the rectum and were found no more frequently in one group than in the other

Preoperative diet and sedation were identical for the two groups

OPERATIVE PROCEDURE

Hemorrhoidectomy was performed by anatomic dissection (modified Milligan-Morgan procedure) No sutures were employed to approximate the cut mucocutaneous edges This operation was particularly adapted to this study because it left large areas denuded of mucosa and skin Hence the rapidity of healing and regeneration was easily observed, and the effect, if any, of the drug was most readily assessed

Under spinal anesthesia, the patient was placed in the prone position, and the area about the anus was cleaned with alcohol and was sprayed with either merthiolate solution or another suitable antiseptic The patient was draped, and the anus was gently dilated with one to three fingers The hemorrhoids were identified, and they were successively removed as follows

An Allis clamp was placed on an external hemorrhoid and another on the skin, about 1 inch (2.5 cm) distal to the hemorrhoid and in a line with it to serve as guide The corresponding internal hemorrhoid was clamped near its base with the tip of a curved Kelly clamp A suture-ligature was tied about the base of the hemorrhoid, and the excess length of the suture was retained for later use Then commencing $\frac{1}{2}$ inch (1.2 cm) distal to the external hemorrhoid, an incision was made along each side of the hemorrhoid and continued as far as practicable in the mucosa toward the suture-ligature By a combination of sharp and of blunt dissection, the hemorrhoid was separated from its bed In so doing, the integrity of the sphincters was maintained When the dissection had proceeded to within $\frac{3}{8}$ inch (1.4 cm) of the suture-ligature, one end of this suture was carried on a needle once through the cut edges of the mucosa, tied and then tied around the entire stump of the hemorrhoid The mass distal to the ligature was cut off Hemostasis of the hemorrhoidal bed was obtained by pressure and, when it was found necessary, by additional ligatures, varying in number from one to three Few were found necessary

The same procedure was repeated on the remaining hemorrhoids, and care was taken to leave bridges of $\frac{1}{4}$ inch (0.6 cm) to $\frac{1}{2}$ inch (1.2 cm) of intact skin and mucosa between dissected areas Any external hemorrhoidal tissue remaining was excised or was punctured by undermining the mucocutaneous bridges No 1 plain catgut (Curity brand or a comparable size of other manufacture) was employed throughout A

gauze pack lubricated with 1 per cent nupercaine hydrochloride ointment was inserted into the rectum, and a pressure bandage was applied externally In cases 7 and 9, sulfathiazole ointment (1 per cent) was employed on the pack as a lubricant It was also applied externally during the postoperative period in these 2 cases

Postoperative care was identical for the two groups, except for the previously mentioned laboratory procedures in the case of the patients given succinylsulfathiazole Also, the control patients received liquid petrolatum, as has been indicated, whereas it was not given to those receiving the drug

All patients were examined practically every day They reported the number and the character of their bowel movements and the degree of associated tenderness Excessive bleeding was noted, as well as loss of appetite and nausea or vomiting They were inspected for external edema and for evidence of healing in the rather large wounds of the perianal skin Starting with the seventh postoperative day, digital and anoscopic examinations were made every other day Tenderness, healing and congestion of the anorectal skin and mucosa were thus evaluated

TOXIC MANIFESTATIONS

No toxic symptoms were manifested while succinylsulfathiazole was administered preoperatively The following were observed on the first and succeeding postoperative days

Loss of appetite was noted in 7 patients of the 10 receiving succinylsulfathiazole for an average of three days' duration Of the controls, 5 had the same complaint for an average of two days

Nausea was felt by 7 of the patients receiving the medication for an average of two days, as compared with 3 control patients who were nauseated for one day each

Vomiting was observed in 3 patients given the drug, as compared with 1 control All of these had this symptom for one day, except 1 patient receiving succinylsulfathiazole, who vomited on two days

Since the control group differed from that receiving therapy only in the frequency and the duration of the postoperative complaints just mentioned, it is questionable whether these can be considered true toxic symptoms They may represent aggravation, by the large volume of medication administered, of a slight functional gastrointestinal irritability associated with this operation In the last 3 cases the method of administration of the drug by means of 0.5 Gm capsules was changed by dissolving the doses of succinylsulfathiazole in peppermint water alkalized with sodium bicarbonate Approximately the same rate of "toxic" symptoms was noted in

these 3 patients as in the preceding 7 who received capsules

In the first patient given succinylsulfathiazole (case 1), undue alarm was caused by loss of appetite and by moderately severe nausea and vomiting on the first postoperative day. The drug was then discontinued. The reaction of

leucytopenia and anemia developed. This patient had a history of bruising easily. There was no history of previous sulfonamide therapy. On the eighth postoperative day, after receiving the drug fifteen days, he suddenly manifested a white blood cell count of 4,700 with 40 per cent polymorphonuclears and 55 per cent lymph-

*Results Observed**

	Controls										Patients Receiving Succinylsulfathiazole									
	2	4	6	8	10	12	14	16	18	20	1	3	5	7	9	11	15	17	19	21
Case Number	31	32	21	26	28	27	23	19	35	21	24	27	37	23	31	29	18	23	32	23
Age of Patient	110†	420‡	327	378	419	299	327	348	450	458										
Total dose of drug in grams	0.26	0.25	0.25	0.26	0.24	0.26	0.25	0.25	0.25	0.25										
Maintenance dose per Kg of body weight	5	7	5	7	7	6	6	7	7	9										
Days of preoperative therapy	3	3	4	3	4	3	4	4	4	3	3	3	3	3	3	5	3	3	3	3
Number of hemorrhoids excised	1	3	3	4	2	3	2	2	2	1	1	2	1	3	1	1	2	1	2	2
Postoperative days before first bowel movement	1	1	2	1	3	1	1	1	2	2	1	2	1	1	2	2	1	1	1	1
Average number of postoperative bowel movements daily	1	1	1	1	2	1	3	1	0	0	1	0	2	1	1	0	0	0	1	1
Days of severe rectal pain	6	8	14	9	2	4	3	3	5	0	5	8	0	6	5	0	4	0	9	4
Days of severe tenderness on bowel movement	5	3	6	11	13	11	7	12	7	2	12	3	3	12	8	>12	5	8	14	9
Days of discernible anal edema	>17	>14	>16	>11	>13	>13	>16	10	9	0	>14	9	>12	>13	>15	12	7	7	>17	>12
Days of moderate tenderness on digital examination	17	>14	>16	>11	13	13	>16	>14	>10	13	9	30	12	0	13	12	10	>13	>17	>14
Days of moderate congestion of mucosa	17	12	8	>11	11	14	14	15	9	>13	14	21	11	13	15	11	>12	>13	12	12
Days to near healing externally	17	>14	16	11	13	13	12	12	10	13	14	30	12	9	13	12	10	11	>15	9
Days to near healing internally	18	15	17	12	14	15	17	16	15	14	15	55	13	15	16	13	13	13	18	14
Postoperative days to discharge																				

* > indicates that symptom was still present or that near healing was not yet attained on the patient's discharge from the hospital

† Administration of the drug was discontinued on the first postoperative day

‡ Granulocytopenia and anemia developed

this patient, therefore, could not be considered in the postoperative evaluation of the drug, although he was observed with the others.

The level of sulfonamide compound in the blood, free and combined, was repeatedly less than 2 mg per hundred cubic centimeters of blood in all cases. Crystals of the compound were never found in the urine.

Significant changes were noted in the blood picture only for patient 3 in whom granu-

ocytes. The red blood cell count was 3,300,000 and the hemoglobin content 76 per cent (Heligge). The blood counts improved in the next four days, so use of the drug was not discontinued. Then on the twelfth postoperative day after nineteen days of therapy, another low count was obtained—white blood cells 4,100, with 41 per cent polymorphonuclears and 58 per cent lymphocytes; red blood cells 3,900,000, with 70 per cent hemoglobin. Administration

of succinylsulfathiazole was discontinued on this day. The following day an equally low blood count was reported. The counts increased spontaneously thereafter, but abnormally low readings were again obtained on the nineteenth, twentieth, thirty-first and thirty-sixth postoperative days, with low normal counts in the interim. On the twenty-fifth postoperative day the patient was given liver extract (50 U S P units at first and then 20 units intramuscularly every other day for several weeks). Finally the blood count became stable. From the fiftieth to the sixtieth postoperative day it averaged white cells 6,200, with 50 per cent polymorphonuclears and 44 per cent lymphocytes, red cells 3,700,000 and hemoglobin 75 per cent. When questioned, the patient complained of some lassitude and some anal burning due to a persistent postoperative anal fissure. At the time this is written, the fissure appears to be healing, and in all other respects the man is well and active.

RESULTS

The results are summarized in the table.

Four of the 10 patients given succinylsulfathiazole had no severe postoperative pain, 2 of the same number of controls likewise had no severe pain.

Three patients receiving the drug did not have marked tenderness associated with defecation postoperatively, as compared with 1 control.

Marked perianal edema was present in 2 patients receiving succinylsulfathiazole, 1 of whom displayed this reaction for four days and the other for one day. This degree of edema was observed in 5 of the control patients, in 1 for two days and in the others for one day each. The duration of perianal edema, when recorded as the least discernible cutaneous distention present, averaged about eight postoperative days for each group.

Evaluation of the postoperative course in terms of tenderness to digital examination, of external and internal healing and of congestion of the anus and rectum cannot be expressed statistically because many patients were discharged before complete relief of all of these symptoms was reached. Consideration of the figures, however, confirms the clinical impression that there was no appreciable difference in the rate of healing

or in the resolution of inflammation in the two groups.

One patient receiving succinylsulfathiazole (case 17) had a fairly severe postoperative hemorrhage, which was readily controlled by repacking. None of the controls bled to any extent. As an occasional hemorrhage will be encountered after this procedure, 1 instance is not significant.

With the exception of patients 1 and 3, who did not have the full course of therapy, the patients receiving the drug were discharged to full duty in an average of fourteen days postoperatively. The controls were discharged in fifteen days' average time.

COMMENT

After hemorrhoidectomies, the individual variation of postoperative course is great. To prove a statistically valid difference between any 2 groups of patients subjected to hemorrhoidectomy would require studies of at least several hundred persons. Nevertheless, if succinylsulfathiazole therapy is of great practical value for such patients it should have been apparent in this small controlled group. Although the figures reported appear to indicate a somewhat more comfortable average postoperative course when succinylsulfathiazole is used, the series is too small for these figures to be statistically significant. In any case, the results are not striking, nor do they appear to justify the use with minor surgical procedures of a drug such as this, with toxic potentialities.

These results are probably due to the fact that succinylsulfathiazole is ineffectual against certain of the organisms present in the stool. On the other hand, even if a drug were available which would eliminate all potentially pathogenic intestinal organisms, it is possible that the natural resistance to infection of wounds in the anorectal region is so great that production of a sterile field would not hasten their healing.

SUMMARY AND CONCLUSIONS

Succinylsulfathiazole has been reported by other physicians to be the drug of choice for the treatment of bacillary dysentery and for use before and after surgical operations on the large bowel.

A trial series of 20 patients were subjected to hemorrhoidectomy, 10 receiving the standard dose of succinylsulfathiazole and 10 being controls

This series included 1 patient who manifested a mild, asymptomatic, transitory, recurrent

granulocytopenia and anemia after fifteen days of therapy

It is concluded that the use of succinylsulfathiazole as preoperative and postoperative therapy in hemorrhoidectomy does not promise to be sufficiently advantageous to justify the risk of its occasional toxic manifestations

CORRECTION

In the article by Dr Robert R Linton entitled "Two-Stage Operation for Carcinoma of the Transverse Colon Producing Duodenocolic Fistula Report of Two Cases," which appeared in the March issue (*ARCH SURG* 48 197, 1944), credit for the first successful extirpation of the head of the pancreas for carcinoma of

the head of the pancreas was given to Dr Whipple, whereas it should have been given to Dr Alexander Brunschwig, who published the first report of a case in which this operation was used (*Surg, Gynec & Obst* 65 681, 1937)

TRAUMATIC RETROPERITONEAL RUPTURE OF THE DUODENUM

PRESENTATION OF A CASE AND REVIEW OF LITERATURE

LIEUTENANT (jg) MURRAY L JOHNSON (MC), USNR

Traumatic surgery at the present time is of great interest to physicians. Traumatic retroperitoneal rupture of the duodenum, though rare, is a condition well worth attention. Reports show plainly that too frequently operation is delayed and that the lesion may be missed at operation, and that the prognosis is poor because of these factors. Thus it behooves every surgeon who is called on to treat patients as surgical emergencies to have some established knowledge of duodenal ruptures into the retroperitoneal tissues and to be able to find an occult lesion when exploring the peritoneal cavity. He will be helped by knowledge of technical factors gained from reports of successful or unsuccessful cases.

Reports¹ from the present conflict have recorded cases of intestinal rupture from "immersion blast force." Study of these reveals the mechanics of many of the retroperitoneal duodenal injuries. Experimental and physical data suggest that intestinal rupture caused by immersion blasts is due not to the first impulse of the blast but more likely to the secondary pressure and concussion effect of actual movement of water away from the scene of underwater explosion. These forces have been reported as acting up to a distance of several hundred feet. There are also undoubted cases of rupture due to crushing of the duodenum against the vertebral column. Many authors have felt that a

crushing force was responsible for a majority of intestinal ruptures, but with reports of rupture by blast force this mechanism becomes important, particularly in the duodenum where almost its entirety is in a protected area. Also the pathologic findings are those to be expected when a "blow-out" occurs—no contusion of the duodenal wall, the mucosal edges not injured and the location of the retroperitoneal rupture of the duodenum most frequently away from the vertebral column. Concomitant injury of the pancreas is rare, and this would not be so if most of the injuries resulted from crushing by direct force. The forces reported to produce retroperitoneal rupture of the duodenum are usually a sudden blunt blow to the abdomen, as the kick of an animal, not necessarily over the duodenum, and sudden squeezing, as when a person is caught between two vehicles, or falls from moderate heights.

The force necessary to rupture a normal bowel is surprisingly low. Andrews² found that a force of 6 to 10 pounds (2.7 to 4.5 Kg) will rupture the intestine in man. Since the pylorus is at one end of the duodenum and the superior mesenteric artery and root of the mesentery press on the fixed duodenojejunal flexure at the other end, producing a closed system, with proper direction of opposing forces rupture will occur.

Retroperitoneal rupture of the duodenum frequently occurs alone, though of course it may be associated with other serious conditions. In the case I report there was an isolated lesion, producing a clearcut clinical picture, as I did not see the patient until twenty hours after the rupture occurred. The case may well be presented in some detail as a pure case of retroperitoneal rupture of the duodenum due to trauma.

REPORT OF CASE

N W, a 10 year old boy, was admitted to the hospital at 4 10 p m on Jan 23, 1943, complaining of severe pain in his abdomen, right loin and back. The history revealed that at 8 30 p m the previous evening the patient had been struck by an automobile while riding his bicycle. His wind was knocked out, but he soon recovered. He was taken to a local physician, who

From the surgical services of Union Memorial Hospital, Baltimore, and U S Naval Hospital, Charleston, S C

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth are those of the author and are not to be construed as reflecting the policies of the Navy Department.

1 Breden, N P, d'Abreu, A L, and King, D P. Sudden Compression Injuries of the Abdomen at Sea, *Brit M J* 1 144-146 (Jan 31) 1942. McMullin, J J A, Palma, J, Pugh, H L, Gates, R, Ecklund, A M and Hamlin, H. Symposium on Immersion Blast Injuries, *U S Nav M Bull* 41 1-32 (Jan) 1943. Greaves, F C, Draeger, R H, Brines, O A, Shaver, I S, and Corei, E L. An Experimental Study of Underwater Concussion, *ibid* 41 339-353 (March) 1943. Friedell, M T, and Ecklund, A M. Experimental Immersion Blast Injury, *ibid* 41 353-363 (March) 1943. Friedell, M T, and Burke, R. Report on the Causation of Blast Injury, *ibid* 41 363-366 (March) 1943.

2 Andrews, E W. Pneumatic Rupture of the Intestine, a New Type of Industrial Accident, *Surg, Gynec & Obst* 12 63-72 (Jan) 1911.

examined him and advised him to return if he did not improve. That night the right side of the abdomen and back became progressively more tender, and he vomited whenever he attempted to take water, there was no blood in the vomitus, however. He had a normal movement of the bowels the following morning, and voiding of urine was essentially normal. Another local physician seen in the morning advised hospitalization. It was after 4 00 p. m. when he was brought into the city and hospitalized. The past history was otherwise unimportant.

He was a well developed and well nourished boy with a flushed face. He was lying quietly. There was some grunting with respiration, and apparently he was in considerable distress. His temperature was 102 F (rectal), the pulse rate 120, respiration 32 and blood pressure 105 systolic and 65 diastolic. His abdomen was slightly distended with generalized spasm, being more rigid on the right side. The points of greatest tenderness were the right costovertebral angle, flank and upper right quadrant of the abdomen. Rebound pain was not as intense as pain on pressure. Liver dullness was normal. The most striking auscultatory phenomenon was the clear transmission of the cardiac sounds over the entire right side of the abdomen (Claybrook's sign). A few borborygmi were heard. There was a small area of ecchymosis slightly to the left of the umbilicus. The leukocytes numbered 14,200, polymorphonuclear forms predominating, hemoglobin was 89 per cent. Urinalysis gave normal results except for a trace of albumin and numerous pus cells with clumps (Two specimens were examined. There had been no previous urinary trouble). A roentgenogram of the abdomen with the patient in the upright position showed "no evidence of air in the peritoneal cavity and the intestines were normal." There was no evidence of emphysema of the tissues in the roentgenograms.

Under brief observation, he did not seem to improve. At 10 p. m., twenty-five and one-half hours after injury, with the patient under ether anesthesia, laparotomy was performed, an upper right rectus incision being utilized. A small amount of straw-colored fluid was present in the peritoneal cavity. The large bowel was distended with gas. The entire large and small bowel, stomach and urinary bladder were examined before a small area of edema and yellowish discoloration of the parietal peritoneum just lateral to the flexion of the duodenum was investigated. No gas was present in these tissues. A small amount of fibrin extended into the peritoneal cavity. The peritoneum was opened and explored with the forefinger, the lesion being easily found on the lower lateral curve of the posterior part of the duodenum. This was mobilized by dividing the reflection of the peritoneum and rolling the duodenum forward, exposing an everted hole about 3 to 4 cm in diameter. The edge of the intestine looked healthy. The ampulla of Vater was palpated about 3 cm away. There were several small areas of fat necrosis and the entire retroperitoneal bed was a yellowish, edematous, homogeneous mass. There was no evidence of injury to the pancreas. The rupture was closed with a Connell inverting suture of zero chromic catgut, reinforced with one row of mattress sutures of fine black silk. The resulting lumen was adequate and the duodenum was allowed to fall back in place. A small muscle-splitting incision was made down to the peritoneum in the right flank for drainage, and since there was a diffuse edematous infiltration of the entire retroperitoneal area one cigaret drain was inserted down toward the pelvis and one up to the lower pole of the kidney. One intraperitoneal cigaret drain was inserted through a lateral stab wound down to the

duodenum along the under surface of the liver. The appendix presented itself and was removed, the stump being tied and inverted. Closure of the abdominal incision was accomplished with chromic catgut and silk skin sutures, 5 Gm of crystalline sulfanilamide being incorporated in the peritoneal cavity and incision. The patient received 500 cc of dextrose solution and 250 cc of plasma on the operating table, and his condition remained good throughout. A nasal stomach tube was inserted, and the patient was returned to the ward. The operating time was one hour and twenty minutes.

His general condition progressively improved. Cyanosis, apparently from the sulfanilamide placed in the wound at operation, developed almost immediately and lasted for thirty-six hours. Sodium sulfathiazole, 2 Gm twice a day, was given for prophylaxis until the fourth day, when administration of oral doses of 1 Gm of sulfathiazole every four hours was begun. With the stomach tube in place, water was given as desired from the day of operation. On January 27 (fifth day) the stomach tube was removed and hourly feedings of 1 ounce (30 cc) of broth alternating with albumin water were started, the amount being increased gradually. On January 29 the patient was put on clear liquid diet, and by February 2, on a regular low residue diet. On January 20 (seventh day) the skin sutures were removed and the drains loosened, and on January 31 all drains were removed. On February 1 a small abscess of the wound was opened, yielding cultures of *Staphylococcus albus*, *Escherichia coli* and beta hemolytic streptococcus. This healed rapidly. Discharge became profuse from the extraperitoneal drainage incision on February 2 (eleventh day). The drainage, though purulent and creamy, was sterile on both aerobic and anaerobic cultures. Carmine given by mouth on February 3 did not come through the drain and there was no evidence of bile (ruling out duodenal fistula), so it was assumed that the discharge consisted of liquefied products of the digestive ferments in the large retroperitoneal area. On February 4 a sulfathiazole rash appeared, the drug was stopped and the temperature, which had been 100 to 102.4 F (rectal) since operation, came down to normal.

Fluoroscopy on February 8 revealed no evidence of the duodenal lesion, and there was free passage of barium down the intestine.

The patient was discharged from the surgical service on February 25, thirty-three days after admission.

On March 4, he was readmitted with fever, leukocytosis and tenderness of the right flank. A residual thick-walled retroperitoneal abscess was drained through the posterior part of the flank. Recovery was uneventful.

COMMENT ON CASE

This case illustrates points brought out in other cases reported during the last half century. In the first place, retroperitoneal rupture of the duodenum occurs with little evidence of external trauma, and the signs of generalized peritonitis do not exist, thus operation may well be delayed unless the syndrome of exquisite tenderness in the costovertebral angle with spreading symptoms leads one to think of the duodenum. The patient is obviously ill, but is not in shock. In the case reported the numerous white cells in the urine I believe were due to the irritation of the intestinal ferments surrounding the kidney and ureter, this has been true in

other cases. At operation the fibrin and the yellow retroperitoneal edema over the lateral curve of the duodenum were indications for further exploration. Proper mobilization of the duodenum was essential to proper identification and closure of the rupture. Regarding drains, the area obviously needing most drainage was the entire right retroperitoneal space, this was done extraperitoneally. Drainage lasted several weeks, a sterile foul creamy pus beginning to exude about seven days after operation. The fact that the patient returned after discharge for drainage of a residual abscess indicates my undue optimism that a single stab wound could drain the entire retroperitoneal space, his return could have been avoided by an additional retroperitoneal drain near the tip of the twelfth rib.

In addition, the contaminated peritoneum overlies an injured duodenum, and a subhepatic drain appeared to be indicated. Pus drained for only one day, the eighth day, then the wound closed promptly. Just how much good the sulfa drugs did is hard to say, but at twenty-six hours, the contaminated area was bacterially as well as chemically soiled. The fact that the condition of the patient was at no time critical and that his improvement was progressive makes me feel optimistic regarding the therapeutic possibilities even when operation is unfortunately delayed.

REVIEW OF THE LITERATURE

Obviously, statistics are made up largely of reports of individual cases, and reports of fatal cases are less likely to appear in print than are those of cases in which treatment was successful. Therefore, I shall confine the presented facts to those that will help in recognizing and treating this condition.

Regarding the incidence of ruptured duodenum, Rowlands³ in 1923 compiled 381 cases, published and unpublished, of rupture of the intestine including 23 of the duodenum, 157 of the jejunum, 158 of the ileum and 43 of the colon.

Schumacher,⁴ in 1910, and Miller,⁵ in 1916 wrote excellent articles reviewing the subject of retroperitoneal rupture of the duodenum. Schumacher collected 91 cases of rupture of the duodenum caused by blunt force, of which 24 were retroperitoneal, and Miller collected 22 additional cases of retroperitoneal ruptures. Of these 46

patients, 37 were operated on and only 5 survived, a mortality of 89 per cent. In 14 of the 37 patients operated on, the lesion was not found. As Miller states, "The large proportion of cases in which the rupture was missed at operation is particularly striking when one remembers that the cases were in the hands of thoroughly trained abdominal surgeons."

Furtwaengler⁶ presented an interesting paper in 1922 discussing late manifestations of retroperitoneal duodenal ruptures, reviewing several cases in which the diagnosis was not reached until duodenal fistulas developed, as late as two months after the original injury. Two of his cases were reviewed, one by Schumacher and the other by Miller. He compiled 118 cases of rupture of the duodenum (anterior or posterior location not specified), in 14 of which, or 11.9 per cent, the patient was cured.

These late manifestations may in truth be due to delayed perforations, the various stages of which have been reported. Meiner,⁷ in 1932, reported a case of retroperitoneal laceration of the duodenum in which no perforation occurred, the patient recovered. Only the outer coats of the duodenum were torn. In Betto's⁸ case, in 1938, a retroperitoneal hematoma was found at operation, about two and one-half hours after injury. Apparently the duodenum was not thoroughly inspected, however, there was no leakage of bile or gas at this time, which would correspond to an incomplete rupture of the duodenum. The area of hematoma was packed with iodoform gauze, and Betto reports that on removal of the gauze on the eighth day drainage of bile and gas began. These manifestations of a duodenal fistula persisted for ten days before the perforation closed spontaneously. Thus one may assume that perforation of an injured duodenum may occur at least several days after trauma, and that bizarre cases, as reported by Furtwaengler, may result when perforation finally occurs in a previously traumatized area.

Leibowicz⁹ in 1930, stated that he had reviewed the literature of duodenal rupture up to that time and that 177 cases of traumatic rupture of all types had been reported. However, no adequate listing or bibliography is presented.

6 Furtwaengler, A. Late Perforation of Duodenum After Contusion, *Deutsche Ztschr f Chir* 175 261-291, 1922.

7 Meiner, E. Retroperitoneal Injuries of Duodenum, *Schweiz med Wchnschr* 62 761 (Aug 13) 1932.

8 Betto, O. Traumatic Contusion and Rupture of the Duodenum, with Report of a Case, *Riv di chir* 4 116-127 (March) 1938.

9 Leibowicz, M. Subcutaneous Injuries of Duodenum, *Zentralbl f Chir* 58 2205-2206 (Aug 29) 1931.

3 Rowlands, R. P. Subcutaneous Rupture of Intestine, *Brit M J* 1 716-717 (April 28) 1923.

4 Schumacher, E. D. Surgery of the Duodenum, *Beitr z klin Chir* 71 482-527, 1910.

5 Miller, R. T. Retroperitoneal Rupture of Duodenum by Blunt Force, *Ann Surg* 64 550-578 (Nov.) 1916.

TABLE 1—Cases of Retroperitoneal Rupture of the Duodenum in World Literature Up to May 1943
Exclusive of Those Reported by Schumacher and Miller

Reported by	Date	Age and Sex	Treatment	Time After Injury Treated	Results	Comment
Straull, A Deutsche Ztschr f Chir 136 167 226 1916	1916	23 M	Expl lap, packing of liver	1 hour	Died after 9 hours	Ruptured liver also present ruptured duodenum not recognized hematoma present
Korte 1904, cited by Mehlhor E Neue deutsche Chir 25 468-484 1917	1917	22 M	Liver packed	22 hours	Died after 5 weeks	Duodenal rupture not found, duodenal fistula developed late
Soderlund, G Nord med Ark 51 191 295 1918	1918	42 M	1 Expl lap 2 Suture 2d day 3 Drainage psoas abscess 5th day	2½ hours	Died after 8 days	Hematoma first operation, bile staining 2d operation not recognized at 1st operation
Harris, W H Canad Praet 47 294 304, 1922	1922	Young M	Drainage only	4 days	Died same day	Retroperitoneal gas present
Harris, W H	1922	Young M	1 Suture 2 Jejunostomy at 12 days	About 20 hours	Died after 19 days	Retroperitoneal gas present duodenal fistula at 10 days
Furtwaengler °	1922	24 F	Closure of duodenal fistula, gastroenterostomy	2 months	Died after 13 days	Pyopneumoretroperitoneum, spontaneous rupture in 5 weeks
Millet 1897, cited by Furtwaengler °	1922	22 M	Drainage only	8 days	Died after 2 days	Ascaris infection
Esau 1911, cited by Furtwaengler °	1922	13 F	Drainage of retroperitoneal abscess, nephrectomy	4 weeks	Died after 6 days	Kidney had been ruptured duodenal fistula developed
Sandahl, C Acta chir Scandinav 59 55 67, 1925	1925	34 M	Suture	2½ hours	Well after 26 days	Retroperitoneal hematoma present
Naumann 1902, cited by Sandahl	1925	39 M	Drainage only	3 days	Died same day	Duodenal rupture not found
von Staplelmohr 1916 cited by Sandahl	1925	32 M	Drainage only	Next day	Died shortly after operation	Duodenal rupture not found fat necrosis present
Harriagton, S W S Clin North America 6 1185-1188, 1926	1926	19 M	Suture	Immediately	Died after 15 days	Duodenal fistula 6th day
Harrington	1926	11 M	Suture, splenectomy	1 hour	Died after 12 hours	Also had ruptures of intraperitoneal duodenum liver and spleen
Rudofsky, F Beitr z klin Chir 40 314 319, 1927	1927	17 M	1 Suture 2 Jejunostomy 7 days	7½ hours	Well after 34 days	Emphysema present, duodenal fistula developed after 7 days
Krogius, A Finska lak sallsk handl 69 809 815, 1927	1927	21 M	Resection 15 cm duodenum, duodenostomy, enteroenterostomy	2 hours	Well after 41 days	Hemoperitoneum from retroperitoneal hematoma evisceration 10th day
Rona, D Gyogyaszat 67 1004 1006, 1927	1927	19 M	Appendectomy suture	Next day	Died after 4 days	Retrocecal phlegmon involving appendix
Woodside, C J A Brit M J 2 1220, 1927	1927	30 M	1 Suture, liver packed 2 Abscess drained 41st day	5 hours	Well after 79 days	Subphrenic abscess developed
Kantor, A Med Klin 25 264 266 1929	1929	38 M	Suture, posterior gastroenterostomy	Immediate	Well	Bile staining present, duodenal fistula developed incisional hernia repaired 2 years later
Davis 17	1930	Young M	Suture, omental graft	2 hours	Well	Area of discoloration medial to kidney
Pedilic I Zentralbl f Chir 57 82 83, 1930	1930	14 M	1 Suture 2 Pseudocyst drained 11th day	6 hours	Well after 39 days	Bile staining and emphysema present pancreatic pseudocyst developed
Ielbowicz, M Zentralbl f Chir 57 1278-1283 1930	1930	26 M	Suture, anterior gastroenterostomy	16 hours	Died after 3 days	Bile staining present
Schmordell, H Zentralbl f Chir 77 1919 1922 1930	1930	Young M	Suture, anterior gastroenterostomy	6 hours	Well after 10 days	Bile staining present
Frechl, E Zentralbl f Chir 58 18-19, 1931	1931	22 M	Suture liver sutured	Immediately	Well after 3 weeks	Retroperitoneal hematoma lacerated liver
Amberger, J Zentralbl f Chir 58 14 15 1931	1931	11 M	Suture	Soon	Well after 7 weeks	Anterior duodenal rupture also
Butler and Carlson 10	1931	24 M	Suture jejunostomy	9 hours	Died next day	Fat necrosis present pain in both testicles unusual sign
Sudhoff 13	1931	17 M	Suture	24 hours	Well after 2 months	Bile staining fat necrosis from bilateral parotitis developed postoperatively
Brizio, G V Polidlinleo (sez prat) 39 261 26, 1932	1932	Young M	Duodenal end closed duodenostomy no drains	8½ hours	Died on 3d day	Retroperitoneal hematoma with fatal laceration of liver and abdominal muscles rupture not recognized
Sereghy F Zentralbl f Chir 59 1165 1167, 1932	1932	21 M	Drainage	20 hours	Died shortly	
Ciminata A Polidlinleo (sez prat) 39 1896-1899 1932	1932	16 M	Suture	4 hours	Well	Bile staining subphrenic abscess formation of exudate
Steinberg, G Arch f klin Chir 171 475-483 1932	1932	24 M	Suture gastroenterostomy	2 hours	Died after 8 days	Bile staining
Köhler 10	1932	10 M	1 End-to-end anastomosis of duodenum 2 Anterior gastroenterostomy 10th day	14 hours	Well after 4 days	Complication

TABLE 1—Cases of Retroperitoneal Rupture of the Duodenum in World Literature Up to May 1943
Exclusive of Those Reported by Schmacher and Miller—Continued

Reported by	Date	Age and Sex	Treatment	Time After Injury Treated	Results	Comment
Lafitte H Arch franco belges de chir 34 117 125 1934	1932	23 M	Suture	9 hours	Well	Bile staining present
Oberaseher H Zentralbl f Chir 60 378-379, 1933	1933	66 M	Suture	1 hour	Well after 21 days	Local anesthesia, also had small prepyloric perforation
Mauro M Ann ital di chir 12 1402 1420, 1933	1933	48 M	Suture	8 hours	Died after 36 hours	Retroperitoneal bloody edema and fat necrosis
Blasker, M Brit M J 1 283 284 1934	1934	Young M	Sutured end to end	2 hours	Well	Retroperitoneal bile and hematoma duodenum 7/8 ruptured, pancreatic fistula for short time Anterior and posterior rupture
Krsek H Bratisl lekar listy 14 390-394, 1934	1934	18 F	Exploratory laparotomy	7 hours	Died on table	
Krsek H	1934	30 M	No operation	1 hour	Died after 1 hour	Head of pancreas mashed
Poindexter ¹¹	1935	51 M	Drained	18 days	Died same day	Large rent in duodenum, retroperitoneal cellulitis
Sperhng and Rigler ¹⁰	1937	19 M	No operation, continuous duodenal suction	20 hours	Well after 13 days	Roentgenogram showed much emphysema
Betto ⁸	1938	15 M	Packed with iodoform gauze	2½ hours	Well after 18 days	Retroperitoneal hematoma, no perforation discovered at operation duodenal fistula at 8 days when drain removed
Wyatt O S Minnesota Med 21 792 1938	1938	3 M	Suture	4¼ hours	Well after 25 days	Retroperitoneal hematoma, also peritoneal leak of exudate
Lure A S Vestnik khir 55 771 772, 1938 Lurje, A Arch Surg 37 808-810, 1938	1938	30 M	Suture, also resection of ascending colon	6 hours	Died after 21 days	Retroperitoneal hematoma emphysema laceration of colon, fistula of colon
Decoulx, P Rev de chir, Paris 77 274 284, 1939	1939	49 M	Drainage	14 hours	Died after 2 hours	Total rupture of 3d portion condition on table very bad retroperitoneal emphysema edema
Zaaijer, J H Nederl tijdschr v geneesk 83 4101 4106, 1939	1939	22 M	Suture	6 hours	Well after 18 days	Edema under and above mesocolon
Holubec K Zentralbl f Chir 66 2580-2590 1939	1939	21 M	Suture packed liver	4 hours	Well after 29 days	Bile staining present, also lacerated liver
Hinton ¹²	1940	13 M	1 Exploratory laparotomy, duodenal suction 2 Post gastro enterostomy at 12 days	6 days	Well	Lesion not found at first operation
Ottenheimer E J, and Gilman, R L New England J Med 222 251 253, 1940	1940	21 M	Exploratory laparotomy	3 hours	Died after 38 hours	Roentgenogram showed emphysema ruptured duodenum not found at operation
Lomazov M G Sovy khir Arkhiv 48 239 241 1941	1941	19 M	Drainage	8 hours	Died after 30 hours	Retroperitoneal emphysema, hematoma and bile staining patient's condition bad before operation was completed
Braun H Zentralbl f Chir 68 1102 1109 1941	1941	18 M	End to end anastomosis of duodenum, Billroth II gastric resection enteroenterostomy	2 hours	Well after 4 weeks	Nearly complete duodenal tear emphysema bile staining present
Braun ¹⁶	1941	50 M	1 Suture 2 Closure of colon fistula at 8 weeks	3 hours	Well after 3 months	Emphysema, blood and bile staining present previous Billroth II posterior gastric resection, 3 years before liver lacerated pneumoair wound disruption and fistula of transverse colon complications
O'Callaghan D Brit J Surg 30 107 112 1942	1942	20 F	Suture liver packed	8 hours	Well after 82 days	Also Colles fracture lacerated liver drainage from wound prolonged
Personal case		11 M	Suture	25½ hours	Well after 54 days	Bile staining fat necrosis present

Kohler,¹⁰ in 1932, reported a case which he states is the eleventh instance of cure of retroperitoneal rupture of the duodenum

Poindexter,¹¹ in 1935, reviewed the literature for the period from 1925 to 1933, presenting 2 cases. He makes a sensible list of points to be considered

¹⁰ Kohler, H Surgical Repair of Retroperitoneal Lacerations Case, Deutsche Ztschr f Chir 237 756-760 1932

¹¹ Poindexter, C A Traumatic Rupture of the Duodenum Texas State J Med 30 561-566 (Jan) 1935

Hinton,¹² in 1940, presented a summary of his review of the literature between 1910 and 1940 and gave the following statistics concerning traumatic rupture of the duodenum 25 cases of anterior rupture, with 13 recoveries, 11 anterior and posterior ruptures, with 6 recoveries, 47 posterior ruptures, with 18 recoveries, 1 with location not stated, in which the patient recovered. This article is brief and the bibliography extremely incomplete

¹² Hinton, D Rupture of the Duodenum by Blunt Trauma, J Internat Coll Surg 3 485-490 (Dec) 1940

There are unusual cases associated with retroperitoneal injuries. I have not included Sudhoff's¹³ second case in my table, as drainage of retroperitoneal abscess occurred one year after the primary injury, no duodenal drainage resulted. Poindexter's¹¹ first case is somewhat unusual. A retroperitoneal abscess drained seven days after injury, and no duodenal drainage resulted. Although there may possibly have been a small duodenal leak in this case, I prefer not to include this and Sudhoff's case in the table.

In Kohler's¹⁰ second case there was bile staining of the retroperitoneal tissues and profuse drainage of bile from the retroperitoneal space for several weeks, but there was no visible rupture of the duodenum when this was mobilized, and apparently no duodenal fistula, but a biliary fistula developed. This would seem to correspond much more to a rupture of the biliary tract as in a case¹⁴ at the Union Memorial Hospital in which the common duct was ruptured by abdominal contusion.

Table 1 is meant to include all bona fide retroperitoneal ruptures of the duodenum which have been reported in the world literature up to May 1943 which were not reported by Schumacher⁴ or Miller.⁵ In the column labeled "treatment," when more than one operation was performed this is indicated by numbering each procedure, otherwise the entire list of procedures was performed at one time.

As can be seen by surveying the bibliography and table 1, there are few reports of cases of traumatic retroperitoneal rupture of the duodenum from this country. Cases reported indicate that with recognition of the condition and with proper treatment results can be good. Therefore I shall present in detail the points of diagnosis that can be utilized as derived from a study of the many complete reports of cases by many authors.

DIAGNOSIS

There is a history of a severe blow to the abdomen, not necessarily over the duodenum, that may not appear to be serious at first. In fact, the patient may be able to walk away from the scene of accident. Then, as extravasation progresses, there is an increasing spread of pain in the right side of the back, right loin and abdomen. Vomiting usually occurs when attempts are made to take anything by mouth but nausea is not a prominent sign. Mild shock and signs suggestive of peritonitis are increasingly manifest, and operation is imperative. Pain in the testicles as a diagnostic sign of retroperi-

toneal duodenal rupture has been reported,¹⁵ but is rarely present. Increase in leukocytes up to 14,000 or more is common but not always present. The urine may contain red cells early from concomitant contusion of the kidney, and not infrequent is the finding of pus with clumping as the intestinal juices extravasate around the kidney and ureter. The roentgenogram may reveal emphysema about the right kidney, emphysema has been reported also as a finding on rectal examination in severe extravasation of gas.

At operation, there is frequently a small amount of "beef broth"-like fluid within the peritoneal cavity. Other intra-abdominal injuries having been ruled out or identified, the area lateral to the duodenum should be inspected. Occasionally fibrin may be found. Edema of the tissues is the most constant finding and increases as the time after injury increases. Staining of the tissues by bile when present is a most important diagnostic sign and ranges from a small green spot overlying a subperitoneal rupture to diffuse yellow staining together with hematoma or edema. Retroperitoneal hematoma is commonly seen. Emphysema is fairly common in this area, extending around the anterior fascial planes in severe cases. Fat necrosis is not often found, interestingly enough. Hemoperitoneum may of course be present when there is an associated lacerated liver, spleen or pancreas or when there is leaking from the retroperitoneal hematoma into the peritoneal cavity.

Of concomitant injuries, laceration of the liver is the most common. When this injury occurs one should not neglect considering the possibility of a retroperitoneal rupture of the duodenum. Rupture of the spleen, multiple ruptures of the bowel, contusion of the pancreas and occasional fracture have been reported with rupture of the duodenum, but it is interesting that this entity exists so often as the only serious injury present.

Table 2 presents some of the most important additional pathologic conditions in our series, to give a general idea of their relative occurrence. It is to be remembered that many reports are not complete, and that therefore this table does not represent the entire number of times these signs occurred.

The prime diagnostic difficulty is similar to that of any intestinal rupture due to blunt trauma to the abdomen, and that is to decide which patient may be safely watched, and which must be operated on immediately. Berry¹⁶ has made this apt statement: "The great majority of such

¹³ Sudhoff, W. Wounds and Injuries of the Duodenum. *Arch f Klin Chir* 164 829-839, 1931.

¹⁴ Finney, J. M. T., Jr. Personal communication to the author, February 1943.

¹⁵ Butler, E., and Carlson, E. Pain in Testicles. Symptom of Retroperitoneal Traumatic Rupture of Duodenum, *Am J Surg* 11 118 (Jan) 1931.

¹⁶ Berry, J. Diagnosis and Treatment of the Intestines, *Brit M J* 2 643 (O).

cases (abdominal contusion) recover without operation But a blow upon the abdomen, followed by severe and continuous localized pain and marked local tenderness, indicates almost always rupture of the intestine These symptoms alone are usually sufficient to demand exploration, especially if muscular rigidity be present as well" In a retroperitoneal rupture signs demanding operation are less likely to present themselves early owing to its occult position The peritoneal cavity is typically not invaded by the extravasation As a rule, operation is performed sooner when such invasion has occurred



Mobilization of duodenum by the division of the peritoneum and rolling the duodenum forward exposing hole

TREATMENT

It is obvious that on reasonable suspicion of retroperitoneal rupture of the duodenum, operation should be performed immediately In most of the cases in which cure is obtained the patients are operated on within the first ten hours after rupture although, as my own case illustrates, more than twenty-four hours may elapse with a successful conclusion

A list of cases in which various procedures have been successful may be of aid, although in any case the surgeon must make an intelligent effort to overcome the existing lesion by reestablishing normal function

At operation proper exposure is the most important single factor, both in determining the extent of the lesion and in its repair For lesions down as far as the inferior flexure of the duode-

num Kocher's maneuver of mobilizing the duodenum by lateral incision of the peritoneum, as shown in the accompanying illustration, is best as it can be rapidly done, allows excellent exposure of the retroperitoneal duodenum and is relatively safe For lesions of the inferior flexure of the duodenum, lying in the submesocolic area, approach by retracting the colon cephalically and dividing the mesocolon will give excellent exposure and in fact is recommended by some authors as the procedure of choice Here, however, the middle colic and superior mesenteric vessels lie close and the technical hazard is thus increased

When the lesion has been identified, as a rule the less done the better the chance of the patient to recover Simple suture obviously fulfils this criterion In the case here reported, as in most of those described, the mucosal edges were clean, signifying a blowout effect, not a crushing lesion of the bowel, such a lesion is amenable to suture as the surgeon desires, remembering that there

TABLE 2—Simultaneously Occurring Pathologic Conditions in Series of Cases Under Consideration

	No of Cases
Retroperitoneal bile staining	16
Retroperitoneal hematoma	13
Retroperitoneal emphysema	13
Rupture of liver	9
Fat necrosis	5
Intraperitoneal rupture of bowel	4
Contusion of pancreas	1

TABLE 3—Successful Procedures Reported

	Schumacher ⁴ 1910	Miller ⁵ 1910-1916	Present Report 1916-1943
Simple suture	1	1	16
Suture and omental graft			1
Suture and gastroenterostomy		1	2
End to end anastomosis			2
End to end anastomosis, Bilroth II gastric resection, enteroenterostomy			1
Resection of injured duodenum with duodenojejunostomy		1	
Resection of duodenum with duodenojejunostomy and enteroenterostomy			1
Resection of duodenum with duodenojejunostomy and gastroenterostomy	1		
Continuous duodenal suction with late gastroenterostomy			1
Continuous duodenal suction			1
Packing of injured area			1
Total survivals	2	3	26
Total cases reviewed	23	22	52

is no peritoneal surface and its sealing effect is not present I think the omental graft as employed in a case by Davis ¹⁷ is an improvement,

17 Davis, C B Injury to Abdomen with Explosion of Viscus, S Clin North America 10 265-266 (April) 1930

to be used if there is any doubt as to the efficacy of closure. Duodenal fistula is a common sequel.

There have been several instances of nearly complete or complete severance of the duodenum, which can occur subperitoneally, and end to end anastomosis has been successful. In one such case,¹⁰ obstruction of the anastomosis occurred and a secondary gastroenterostomy was necessary. Regarding a complementary gastroenterostomy, which has been advised by some surgeons as proper in all cases, I believe that this is to be reserved for those cases in which the repair has impinged to an obstructive degree on the lumen of the bowel. Reliance should be placed on an indwelling stomach or duodenal tube to put the repaired bowel at rest in the usual case. Anterior and posterior gastroenterostomies have alike been utilized as complementary therapy.

Braun¹⁸ suggested performing a gastric resection in lieu of gastroenterostomy as the incidence of jejunal ulcers will thereby be reduced. It is to be remembered here again that this is an added procedure, therefore it would not seem to be the procedure of choice.

When there has been a crushing injury it has been necessary on occasion to resect a portion of the duodenum. This usually obviates any duodenoduodenal anastomosis, for both ends are fixed. Closure of the distal end and anastomosis with a loop of jejunum have been found successful in such cases. One of the most complicated cases in which cure was obtained was that of Enderlen, cited by Schumacher,⁴ in which it was necessary to resect the duodenum from just below the ampulla of Vater to the duodenojejunal flexure. The ends were closed, and a gastroenterostomy was performed. Then, with the patient in satisfactory condition, a duodenojejunostomy was performed to give an outlet for bile and pancreatic juices.

Theoretic considerations concerning possible rupture of the duodenum at the point of the ampulla of Vater have been presented by several authors, in which various procedures of exclusion with reanastomosis of the gallbladder, pancreatic and biliary ducts to the jejunum or stomach are advanced. Statistics do not show any ruptures at this point, however, which may be due to the physical strength that does not give way to internal or external forces.

Drainage is a most important part of the treatment, its importance increasing as the time between injury and operation increases. Because of the nature of the lesion it is mainly in the retroperitoneal space that the cellulitis is located and it may extend to the opposite side and down

into the pelvis. When the duodenum is mobilized a direct peritoneal opening to this area is provided. While the peritoneal cavity cannot be adequately drained, the area overlying the injury can and should be. The extraperitoneal space can be adequately and extensively drained by stab wounds in the posterior part of the flank and lower lateral area of the abdomen, the wounds necessary being of course in direct relation to the extent of infiltration present. Previous authors have not stressed extraperitoneal drainage, but the lateness of operating in the case presented, the extent of the infiltration and the subsequent late development of a retroperitoneal abscess all have made me more interested in this point. One counterincision cannot drain the retroperitoneal space on one side adequately.

Local application and systemic use of the sulfa drugs should be added to the treatment that I have described unless contraindications exist.

Sperling and Rigler¹⁹ presented a case in 1937 in which the diagnosis was arrived at by indirect evidence. Roentgenograms showed emphysema of the retroperitoneal tissues and later, after ingestion of barium, a deformity of the second portion of the duodenum. The physical findings were concordant with a retroperitoneal duodenal rupture. The patient recovered after treatment with simple duodenal suction for ten days, but I believe the gods were smiling here. Extravasation has been prevented at least in 1 reported case (cited by Schumacher⁴) by actual blockage of the perforated area by blood clot. However, this fortunate circumstance is most unusual and in most instances there is a wide open lesion. Thus duodenal suction cannot be accepted as anything more than accessory treatment to proper surgical measures. The roentgenographic evidence of emphysema from a ruptured duodenum is of course a valuable aid in diagnosis, and its presence should mean immediate laparotomy.

It is to be noted that Hinton's¹² patient was treated by continuous duodenal suction for six days before the first operation, at which time the rupture was not found, and that a gastroenterostomy without closing the duodenal tear was performed six days later with successful result.

COMPLICATIONS

Too frequently the cause of death is not given in reports of cases, but, aside from general injuries, there appear to be two primary reasons for unsuccessful treatment—peritonitis and retroperitoneal cellulitis. Table 4 lists other compli-

¹⁸ Braun, H. Rupture of the Duodenum by Blunt Trauma, *Zentralbl f Chir* 68 1102-1109 (June 14) 1941

¹⁹ Sperling, L, and Rigler, L G. Traumatic Retroperitoneal Rupture of Duodenum. Description of Valuable Roentgen Observation in Its Recognition, *Radiology* 29 521-524 (Nov) 1937

cations arising within the abdomen in the series of cases considered in this paper

Pulmonary complications are not unusually frequent. Breakdown of wounds is more common than in routine abdominal operations and is a point against placing drains through the incision.

TABLE 4—*Serious Intra-abdominal Complications (Excluding Cellulitis and Peritonitis)*

Condition	No of Cases	Comment
Duodenal fistula	8	Three recoveries
Pancreatic fistula	1	Recovery
Subphrenic abscess	1	Recovery
Duodenal obstruction	1	Recovery, following end to end anastomosis
Pancreatic pseudocyst	1	Recovery
Fistula of colon	2	Right portion of colon resected in 1 case

SUMMARY AND CONCLUSIONS

Retroperitoneal rupture of the duodenum by blunt trauma to the abdomen is an unusual condition which is difficult to treat successfully. Diagnosis even during operation is often missed. The literature between 1916 and 1943 reveals 52 cases, in 26 of which cure was obtained. In 7 of these 52 cases the lesion was not found at operation.

One additional case of retroperitoneal rupture of the duodenum presented is the thirty-second case of successful treatment reported in the entire literature on the subject.

It is necessary to individualize the treatment in each case, but the basic factors, besides general preoperative and postoperative care, to be considered in curing a patient with retroperitoneal rupture of the duodenum are

- 1 Correct diagnosis at operation. Whenever edema, staining by bile, hematoma or emphysema occurs over the retroperitoneal area of the duodenum, the surgeon must explore.

- 2 Closure of the rupture.

- 3 Short circuiting operation, only if the closure of the rupture produces obstruction.

- 4 Proper drainage of the peritoneal cavity and the retroperitoneal space.

- 5 Stomach or duodenal tube to put the traumatized area at rest.

- 6 Intelligent use of the sulfa drugs.

Many complications may arise following treatment of retroperitoneal rupture of the duodenum, the most serious of which are peritonitis, retroperitoneal cellulitis and duodenal fistula.

ORAL ADMINISTRATION OF DIETHYLSTILBESTROL FOR PROSTATISM

A CLINICAL EVALUATION

WILLIAM KLEIN, M D AND BERNARD NEWMAN, CH E, M S
NEW YORK

A frequent and persistent complaint of the aged man is inability to rest at night due to frequent urination. In our institution, we have an opportunity to observe over 200 men whose ages range from 67 to 98 years. Many of these men are unwilling to undergo prostatectomy or are poor risks for such a procedure. Hence we have attempted to alleviate their condition by the oral administration of diethylstilbestrol.

Noble¹ soon after the effects of diethylstilbestrol had been noted reported that male rats after treatment with diethylstilbestrol exhibit atrophy of the testicle and decrease in the size of the seminal vesicles and the prostate. Mellish, Baer and Macias,² using an experimental group of 39 rats which had received implantations of 10 mg of diethylstilbestrol twenty-eight days previous to autopsy, found the mean weight of the prostate to be 20 mg. In an untreated group of 23 controls they observed the average prostate to weigh 102 mg.

Huggins and Clark³ noted that after periodic injections of large doses of diethylstilbestrol into 7 senile dogs the prostate glands decreased in size.

One of the earliest reports on the treatment of benign prostatic hyperplasia in human beings is that of Kahle and Maltby.⁴ These observers stated that treatment with testosterone not only has no effect on the hyperplastic prostate but at times seems actually to stimulate the gland to further hyperplasia. Hence the authors resorted

to the use of diethylstilbestrol. They used as their experimental group 14 men between the ages of 51 and 80 years, who were treated with diethylstilbestrol parenterally. Their nocturnal frequency of urination and other concomitant symptoms were ameliorated, and in every patient a decrease in the size of the prostate was noted on rectal examination. The authors reached the conclusions that the administration of estrogenic substances produces definite changes in the glandular elements of the hyperplastic prostate, that moderately enlarged glands regress to normal size and even atrophy with complete relief of symptoms, while very large glands decrease in size and in an appreciable number of cases even return to normalcy and that hyperplasia of the prostate can probably be controlled by adequate therapeutic and maintenance doses of diethylstilbestrol.

A review of the literature on the interaction between the prostate, the pituitary and the gonads and the treatment of prostatic hyperplasia with diethylstilbestrol dipropionate was reported by Colon.⁵ He treated 9 patients with hypertrophy of the prostate by intramuscular administration of diethylstilbestrol dipropionate. All of his patients unquestionably benefited. The number of nocturnal urinations decreased, and the longer periods of rest had a marked beneficial effect on their well-being. Rectal examination of all his patients showed a definite decrease in the size of the prostate, and catheterization revealed a decrease in the amount of residual urine. While Colon also employed prostatic massages as a form of therapy, it is well known that this treatment alone could not account for the results he obtained.

A study was made by us of the effects of the oral administration of diethylstilbestrol on prostatism in old men.

EXPERIMENTAL PROCEDURE

Twenty-five men, ranging in age from 68 to 94 years, were examined. Their chief complaint at the time was frequency of nocturnal urination and other concomitant

5 Colon I E. Tratamiento medico de la hiperplasia prostatica. Bol. Asoc. med. de Puerto Rico 34: 41, 1942.

From the Surgical Division of the Hospital and Home of the Daughters of Jacob.

1 Noble, R. L. Effect of Synthetic Estrogenic Substances on Body Growth and Endocrine Organs of Rat, *Lancet* 2, 192, 1938.

2 Mellish, C. H., Baer, A. I. and Macias, A. C. Experiments on the Biological Properties of Stilbestrol and Stilbestrol Dipropionate. *Endocrinology* 26: 273, 1940.

3 Huggins, C., and Clark, P. J. Quantitative Studies of Prostatic Secretions. Effect of Castration and of Estrogen Injection on Normal and on Hyperplastic Prostate Glands of Dogs, *J. Exper. Med.* 72: 747, 1940.

4 Kahle, P. I. and Maltby, E. Treatment of Hyperplasia of the Prostate with Diethylstilbestrol and Diethylstilbestrol Dipropionate. *New Orleans M. & S. J.* 93: 121, 1940.

disturbances, such as a sense of pressure and pseudo-
priapism

A history of each patient's urinary complaints was taken. A rectal examination of the prostate was made, and the size, consistency, anatomic landmarks and other pertinent data were noted and recorded. The subjects were then catheterized after having voided in order to determine the amount of residual urine.

Specimens of blood were obtained after a fast of at least eight hours, and the following constituents were determined: urea nitrogen, acid phosphatase, sugar and

Subjects were observed biweekly, and oftener when some unforeseen occurrence was reported to the staff. All prostatic examinations were performed by one of us (W. K.).

The table shows, in condensed form, the salient features of our observations.

COMMENT

As mentioned previously, the beneficial effects of diethylstilbestrol on benign hypertrophy of

Summary of Effects of Oral Administration of

Case	Age	Chief Complaint	Rectal Examination	Residual Urine, Cc	Maximum Dosage		Effect of Medication
					Mg. per Day	Period of Medication	
1 B. I.	67	Nocturnal urination, four times, sensation of pressure, occasional dribbling	Very large prostate, soft, anatomic markings normal	Not determined	0.75	9 weeks	Uninterrupted sleep from 11 p. m. to 6 a. m. sensation of pressure and dribbling gone
2 A. S.	86	Nocturnal urination six to eight times, burning and pain on micturition	12/17/42 Large senile prostate soft	120	1	12 weeks	Burning and pain disappeared, nocturnal urination reduced to one time
3 I. S.	77	Nocturnal urination five times	12/17/42 Small prostate, hard	Not determined	5	4 months	Nocturnal urination unimproved
4 A. K.	82	Nocturnal urination four times	12/31/42 Extremely large prostate firm at the periphery	Not determined	2.5	12 weeks	Nocturnal urination reduced to two times
5 S. A.	80	Nocturnal urination five times almost constant dribbling	12/17/42 Moderately enlarged prostate firm	180	2.5	8 weeks	Nocturnal urination reduced to three times, dribbling somewhat less
6 S. M.	76	Nocturnal urination four times	12/17/42 Enormously enlarged prostate soft	Not determined	3	12 weeks	Nocturnal urination reduced to one time
7 B. L.	64	Nocturnal urination eight to ten times continual dribbling	3/2/43 Moderately enlarged prostate very hard	Could not be obtained patient had hypospadias	3	9 weeks	Nocturnal urination diminished, dribbling less
8 J. G.	85	Nocturnal urination four to five times	1/7/43 Moderately enlarged prostate hard	15	3	13 weeks	Nocturnal urination reduced to two times
9 B. P.	71	Nocturnal urination four to five times	12/28/42 Very large and soft prostate, anatomic markings well defined	50	2	10 weeks	Nocturnal urination reduced to one time
10 A. H.	77	Nocturnal urination seven or eight times	12/17/42 Large and soft prostate	90	3	5 months	Nocturnal urination reduced to three times
11 A. R.	73	Nocturnal urination hourly each voiding preceded by severe spasm	12/22/43 Large and soft prostate, some induration at lower end	Not determined	3	12 weeks	Nocturnal urination reduced to two times
12 A. B.	67	Nocturnal urination three or four times	12/18/42 Moderately enlarged prostate very hard, anatomic landmarks not well defined	60	3	4 weeks	None
13 S. H.	77	Nocturnal urination five or six times	12/17/42 Very large prostate soft	60	4	14 weeks	Nocturnal urination reduced to two times
14 B. S.	81	Nocturnal urination six times	2/2/43 Extremely large prostate soft	50	3	10 weeks	Nocturnal urination reduced to two times
15 L. R.	80	Nocturnal urination two or three times pseudo-priapism	12/18/42 Moderately enlarged prostate normal in consistency	Not determined	2	14 weeks	Uninterrupted sleep through the entire night priapism subsided
16 D. A.	71	Nocturnal urination five times	1/21/43 Much enlarged prostate firm	Not determined	3	16 weeks	Nocturnal urination reduced to two times (large stream)
17 L. H.	71	Nocturnal urination four times sense of pressure	5/12/43 Tremendously enlarged prostate, soft	Not determined	3	5 weeks	Nocturnal urination reduced to two times, no sense of pressure

total and esterified cholesterol. Twenty-four hour specimens of urine were collected and preserved with toluene, and the daily excretion of creatine and creatinine was determined.

Administration of small doses of diethylstilbestrol was begun. This substance was administered orally in the form of enteric-coated tablets and was given twice daily, in the morning and in the evening. Patients in this age group are often uncooperative and imbued with some degree of superstition and hence cannot be entrusted with medicine to be taken in privacy. We therefore arranged for the administration of the diethylstilbestrol by the intern staff daily at specified hours.

6 Bought on the open market from a reliable manufacturer.

the prostate have been reported by a number of observers. We were, however, unable to find reports of synthetic estrogens having been administered orally for such a condition. There is an obvious advantage for all concerned if the desired effects can be obtained by giving diethylstilbestrol orally. We were fully aware of the differences between oral and parenteral administration of any drug both in its effects and in its dosage. Since persons show a wide variation in their reaction to diethylstilbestrol, one must determine the dose for each subject, starting necessarily with small amounts. In our series

or cases, the tolerance of the subjects varied so much that no attempt was made to determine a minimum effectual dose or a maximum dose that could be tolerated without unpleasant side reactions

An interesting observation was one that bears out the report of Ravich,⁷ who found that among Jewish patients with hypertrophied prostates the incidence of carcinoma was 1.7 per cent, as com-

or metastatic carcinoma was noted during the period of observation. We are not unmindful of the possible carcinogenic properties of the synthetic as well as the natural estrogens. In the short period during which these subjects were under study, we were unable to observe any carcinomatous effects. The fact that our subjects are of an advanced age group and may die from intercurrent diseases before many years

Diethylstilbestrol on Prostatism in Old Men

Subsequent Rectal Examinations	Complications	Total Time of Observation	Comment
2/18/43 Prostate reduced in size, corresponds to average in a man of 40 years, firmer 4/5/43 Prostate smaller than on previous examination and much firmer	Both breasts indurated and painful at end of nine weeks, medication discontinued, relief in two weeks	6 months	At present patient sleeps through night, feels young again
4/5/43 Prostate markedly decreased in size much firmer	At end of three months painful and indurated breasts, medication discontinued, complete relief in two weeks	6 months	Patient remains free from all symptoms referring to urinary bladder
5/28/43 No change in size or consistency of prostate	None	5½ months	No beneficial effects noted
5/17/43 Prostate reduced to about one half the previous size	None	5 months	Patient in hospital division due to nonpathologic fracture of neck of femur
3/2/43 Prostate somewhat smaller than on previous examination	None	5 months	Patient improved little
3/30/43 Prostate smaller and firmer	Enlarged and painful breasts at end of twelve weeks' medication	6 months	Improvement continues, patient had a transurethral resection done four years previously
5/20/43 Little change in size and consistency of prostate	None	12 weeks	Beneficial effects questionable
4/19/43 No changes noted	Nausea, eructations and anorexia	13 weeks	Complications cleared up in a few days after medication was discontinued
4/5/43 Prostate reduced to about half previous size somewhat firmer	Nausea, vomiting at end of three months' medication	5 months	Improvement continues, gastric symptoms disappeared within a few days after medication was discontinued
6/1/43 Prostate much reduced in size, somewhat firmer	None	6 months	Improvement is slight
4/19/43 Prostate decreased to about half previous size	None	5½ months	Patient refuses further cooperation because he feels well
5/19/43 Condition of prostate unchanged	None	5 months	Patient in hospital, bedridden due to chronic arthritis
4/23/43 Prostate much smaller and firmer, upper pole easily reached	Indurated painful breasts	6 months	Induration and sensitivity of nipples persisted for five weeks
5/17/43 Prostate reduced in size firmer	Development of sublingual adenitis and stomatitis, which cleared up five days after medication withdrawn	4 months	That the adenitis was a complication of diethylstilbestrol therapy is questionable
5/31/43 Prostate somewhat smaller much firmer	None	5½ months	Patient states loss of power for sexual intercourse
6/14/43 Prostate much smaller and firmer	None	6 months	Symptoms only slightly ameliorated
6/17/43 Prostate moderately reduced in size all other findings same	None	5 weeks	More improvement to be expected in the future

pared with 20 per cent among all other patients with a similar condition. His suggested explanation that circumcized men are less prone to carcinoma is interesting. In this institution, there are over 200 men, all of whom are circumcized and whose ages range from 65 to over 95 years. The incidence of prostatic carcinoma among these men is very low, being slightly over 1 per cent. In the group under consideration, no evidence pointing toward either local

affords us but little opportunity to study this phase of the problem.

In evaluating the effect of any medication on persons in an advanced age group, one must take care in interpreting their verbal responses to any inquiry. We were therefore reluctant to treat those patients whose mentality was shrouded. Twenty-three of our group were ambulatory and not under treatment for any other disease. Two were hospitalized (one for chronic arthritis and the other for a nonpathologic fracture). It was observed early in our experiments that those men who were physiologically younger

⁷ Ravich, A. The Relationship of Circumcision to Cancer of the Prostate, *J Urol* 48:298, 1942

than their chronologic age responded to smaller doses of diethylstilbestrol.

It is therefore evident that the dosage will be generally in direct proportion to the degree of senility.

Another observation was that the younger, better preserved subjects were more apt to show complications resulting from diethylstilbestrol therapy than the others. The most frequent complication was changes in the mammary gland. Approximately 16 per cent complained of painful and swollen nipples. Examination revealed that the tissues surrounding the nipples were indurated and tender, while the nipples themselves showed little change. The indurated areas

were not bedridden. The prostate by rectal examination appeared very large and rather soft. The anatomical landmarks were well outlined. Roentgen examination of the long bones failed to reveal any pathologic condition. He was given diethylstilbestrol in doses of 1 mg daily for six weeks. At the end of this period he began to complain of painful nipples and enlarged breasts. Examination revealed that both breasts were enlarged to about the size of those of a girl 12 years old. The nipples were black and sensitive. The left breast was excised and sectioned.

Pathologic Report—A section of the mammary tissue revealed as the most prominent feature cystic changes, which appeared to involve the ducts. These ducts were distinctly cystic and for the most part lined by a single layer of cuboidal epithelium with deeply staining nuclei and clear cytoplasm. In some of the ducts there was a tendency for the epithelium to be multilayered, but this

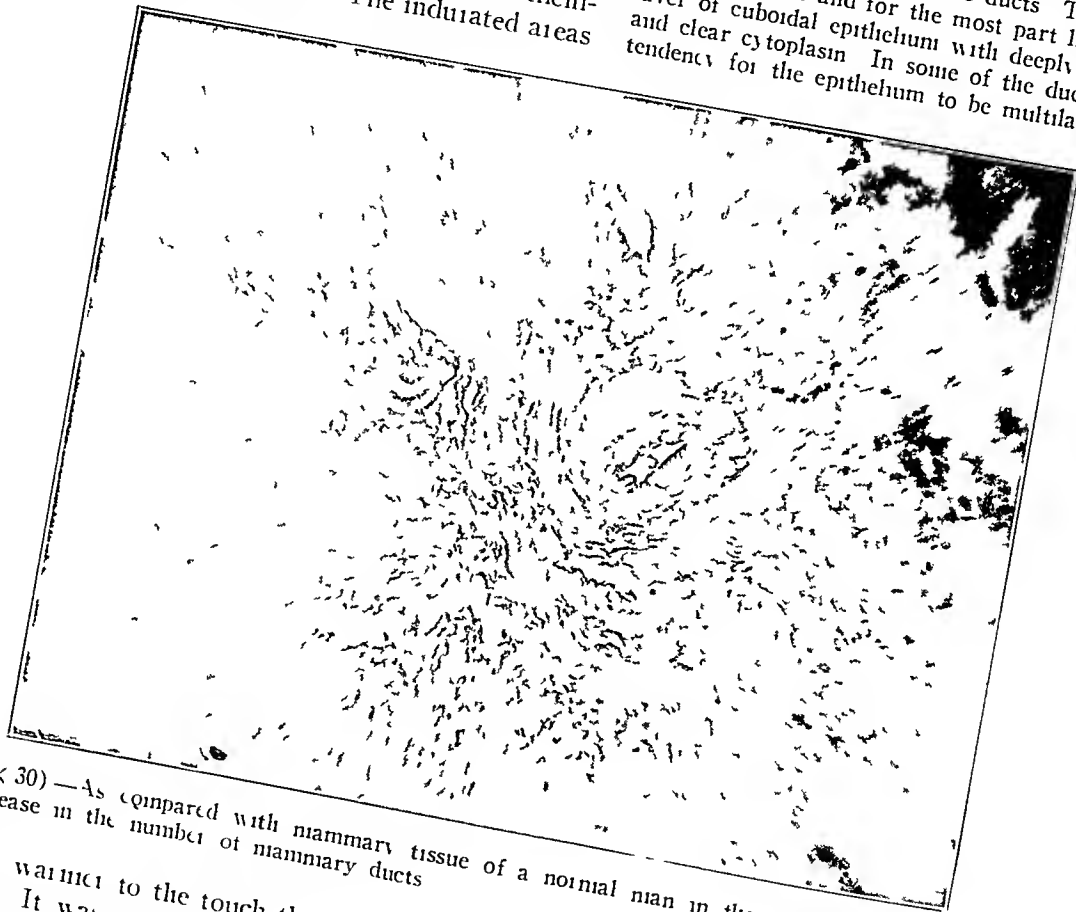


Fig 1 ($\times 30$)—As compared with mammary tissue of a normal man in the same age group, there is an apparent increase in the number of mammary ducts.

were slightly warmer to the touch than the rest of the body. It was not possible to determine at what dose this complication occurred, but at the time our patients complained of this untoward effect their prostatic troubles were markedly improved. Medication was discontinued and within one week the subjective symptoms subsided but the induration persisted slightly longer.

Since the preparation of this paper we have had the opportunity to examine 1 such enlarged breast.

A G aged 79 complained chiefly of nocturnal frequency of urination with occasional priapism. He had to urinate as much as eight times per night. Physical examination revealed a well nourished man alert and

was the exception rather than the rule. In 1 duct, however, there was a distinct multilayering of the lining epithelium, the superficial portion of which, bordering the lumen, appeared to have undergone metaplasia, the cells consisting of what appeared to be squamous cells. There was a moderate infolding of the lining of most of the ducts and the intervening stroma showed some hyalinization and a moderate amount of interstitial edema. The skin overlying the mammary tissue showed no essential pathologic change.

Further Course—Three weeks after the use of the drug was discontinued, the pain in the right breast disappeared and there was a notable reduction in its size.

Another side effect was a gastric disturbance. Only 2 of our 25 patients complained of nausea, eructations and anorexia. (We were aware of

the work of Chamelin and Funk,⁸ whose experiments showed that liver extract reduced the toxicity of diethylstilbestrol, but we did not avail ourselves of this information.) The gastric symptoms were relieved within three days after the medication was withdrawn.

No other complications were noted.

As was pointed out previously, there were wide variations in the tolerance of the experimental subjects to diethylstilbestrol. Some subjects tolerated 5 mg daily for as long as six weeks without ill effects, while others showed gastric or mammary complications within two weeks after taking 1 mg per day.



Fig 2 ($\times 60$)—The ducts are hyperplastic, enlarged and dilated, the adjacent stroma is edematous

Care must be taken that the greatest possible absorption occurs and that no other medication interferes with the maximum effect. Since many of these old men were in the habit of taking liquid petrolatum, which has been shown to interfere with complete absorption from the gastrointestinal tract, this form of medication was stopped. It is also known that diethylstilbestrol is soluble in oil and may pass through the body unabsorbed.

We had hoped that the effect of diethylstilbestrol on the prostate would be to reduce the size of the gland and that the resultant shrinkage would be lasting. We have at the time of

writing 8 subjects whose last dose of diethylstilbestrol was given from three to five months ago. Their prostates have remained reduced in size and the original improvement as to the frequency of micturition and the other concomitant symptoms has persisted. One subject, whose chief complaint was pseudopriapism, was relieved at the end of one month's treatment with 1 mg of diethylstilbestrol daily and his symptoms have not recurred. Our observations are necessarily clinical and we are cognizant of the limitations of clinical evaluation. However, our findings seem to corroborate the report of Kahle and Maltby.⁴ On sectioning prostates of persons

who had been under treatment with diethylstilbestrol they found

- 1 A reduction in the number of papillary infoldings
- 2 A decrease in the size of the acini
- 3 A reduction in the height of the epithelium
- 4 Stratification of the epithelium with and without vacuolization of the cells

Further study of this problem is needed.

The following cases are typical instances of successes and failures of treatment.

CASE 1—B I, aged 67, was well preserved for his age and able to carry on useful work in the institution. His chief complaint was nocturnal frequency of urination—four or five times. Occasionally there was a sense of pressure. Examination per rectum revealed a large, soft prostate with the central groove well outlined. The patient was given 0.5 mg of diethylstilbestrol daily.

⁸ Chamelin, I, and Funk, C. Action of Liver Extracts in Counteracting Toxic Effects of Diethylstilbestrol and Sulfamylamide. *Arch Biochem* 2, 9, 1943.

At the end of ten days the patient reported that the sensation of pressure had disappeared and that he now was getting up only once a night. The dose was increased to 0.75 mg a day for one week and then to 1.25 mg for a week. At the end of six weeks' treatment, the patient reported that he had been sleeping from 11 p. m. to 6 a. m. without interruption. Only on rare occasions he had a sensation of pressure during the day, but he complained of pain in both nipples. Examination revealed that both areolar areas around the nipples were indurated and tender. The prostate was reduced to about half the size but appeared somewhat harder in consistency. All medication was then discontinued. Within two weeks all subjective and objective signs of induration around the nipples had disappeared. The patient was reexamined three months after administration of diethylstilbestrol had been stopped. The pros-

The patient reported that the burning and the pain on urination had disappeared and the amount of urine voided each time was greatly increased. The dose was increased to 3 mg daily for a month. At the end of this time, nocturnal urination was reduced to twice, but the subject complained of painful sensations in both breasts. Examination revealed the usual induration and sensitivity in the tissues around the nipples. Treatment with the drug was then discontinued. The patient was examined two months later. Findings at that time were as follows: The prostate was greatly reduced in size and firm in consistency, all mammary signs had disappeared, the patient still urinated twice nightly.

CASE 3—I S., aged 77, was examined on Dec 17, 1942. His chief complaint at that time was nocturnal frequency of urination—five to six times—with no pain. Rectal examination revealed a rather small prostate,



Fig 3 ($\times 90$)—The lining cells of the ducts are duplicated, their nuclei are hyperchromatic. A thin secretion is present within the lumen.

tate appeared even a little smaller than at the last examination and none of the urinary complaints had recurred.

CASE 2—A S., aged 86, had had a suprapubic prostatectomy fifteen years previously. The improvement after that operation was only moderate. The patient still had to urinate twice nightly. The frequency of nocturnal urination increased as time progressed, until at the time of our first examination, on Dec 17, 1942, urination occurred every two hours accompanied by pain and a burning sensation. Examination at this time revealed a large prostate, soft in consistency with anatomic markings not well delineated. There was a moderate stricture at the anus, apparently caused by a hemorrhoidectomy some years previously. The patient was given 0.75 mg of diethylstilbestrol daily. One month later he reported that there was definite improvement. The same dose was given for another month.

firm in consistency, with normal anatomic landmarks. It was rather surprising to find such a small, hard prostate. The patient was then given a general physical examination to rule out the possibility of cancer. No signs of either local or metastatic carcinoma were found. The blood acid phosphatase was within normal limits. The patient was given 0.5 mg of diethylstilbestrol daily. After taking the drug for one month, he reported no improvement. The dose was then increased to 1.5 mg daily for one month, after which time no improvement was reported. The dose was then increased to 3 mg a day for a month with but little subsiding of his symptoms. The amount was finally increased to 5 mg daily for three weeks. This time there was a reduction in frequency of urination to three to four times nightly. Examination of the prostate at this time showed it to be somewhat smaller but with no distinct change in consistency.

This case illustrates the point that pronounced beneficial effects cannot be expected in the shrunken, hard prostate

From a study of the accompanying table and the cases reported, it may be noted that considerable improvement may result from comparatively small doses of diethylstilbestrol in favorable cases, while in other cases large doses may fail to give the desired effect. It is therefore important to treat each patient individually and the doses should be regulated by close observation of his progress. As a general statement, we may say that in a person who is well preserved for his age and mentally alert and whose prostate is of the general hyperplastic type (senile hyperplasia) favorable results can be expected with this particular kind of estrogen while in one who is suffering from advanced arteriosclerosis and its concomitant mental state or in one whose urinary obstruction is due to fibrous bars and sclerosis of the wall of the bladder good results cannot be expected.

As may be seen from the table, only 17 cases are tabulated. The other 8 cases have not been observed for a sufficient length of time to be included in a summary of results.

The criterion for success or failure was, of course arbitrary. We were, however, reluctant to classify patients as improved unless the number of nocturnal urinations was reduced by at least 50 per cent. In the light of this criterion, there were 71 per cent who were improved or completely relieved. Of the remaining 29 per cent, only 1 subject showed no change in either

the number of nocturnal urinations or the condition of the prostate. The other 6 patients showed varying degrees of improvement. It is therefore evident that the majority of men in our series were greatly benefited by this form of therapy. Two of the subjects complained of prostatism with an average frequency of nocturnal urination of five times. They had had suprapubic prostatectomies ten and three years ago respectively.

Complications occurred in approximately 25 per cent of the patients. Eighty per cent of these complications consisted of enlargement of the mammary glands, while the rest were gastric. None of these were severe enough to cause disability or to require confinement in the hospital. These complications occurred only when the maximum dose for the person was continued from three to four weeks.

SUMMARY

Twenty-five patients with prostatism were treated by oral administration of diethylstilbestrol. The majority showed distinct improvement.

Complications occurred in 25 per cent of the patients, all of which cleared up soon after medication was discontinued.

The resultant shrinkage of the prostate remained for at least six months. Whether this shrinkage is permanent will be shown by future examinations.

Dr S. Seidenberg, senior resident physician, and Miss Annette Block gave their assistance.

PROSTHETIC RESTORATIONS FOR THE BREAST

TECHNIC USING SPONGE RUBBER

ADOLPH M BROWN, M D

CHICAGO

A prosthesis (*πρόσθεσις*, a putting to, from *προστίθημι*, to put to) is an artificial substitute for any missing part of the body. Since most such corrections are for facial deformities and defects much of the literature and the interest is concerned with facial restorations.¹

In 1942 I² described a prosthesis for the restoration of the defect caused by the amputation of the breast and presented the technic of its construction. That paper was concerned with the restoration of the breast after surgical ablation. With modern education patients suffering from diseases of the breast seek earlier consultation, carcinomas of the breast are seen in and removed from younger persons. For want of something better, women who have undergone amputation of the breast attempt esthetic correction of the defect by wearing brassieres filled with various materials e g cotton, lamb's wool, upholsterer's hair and goose down. The brassieres must be worn rather snugly to give a sense of firmness and security. Perspiration is therefore troublesome, and swimming, beach lounging and dancing become esthetically hazardous pastimes for these women.

Another class of patients who seek cosmetic correction are women with congenital atrophy or absence of the breasts. They attempt to give the outline of the breasts a semblance of acceptability by wearing brassieres filled with soft materials.

1 Brown, A M. Correction of Facial Defects with Latex Prostheses, *Arch Otolaryng* **35** 720-731 (May) 1942, Extensive Mutilating Facial Defect. Cosmetic Correction with Latex Mask Surgery **12** 957-961 (Dec) 1942. Bulbulian, A H. An Improved Technique for Prosthetic Restoration of Facial Defects by Use of a Latex Compound. *Proc Staff Meet, Mayo Clin* **14** 433-439 (Jul 12) 1939. Lederer, F L. Prosthetic Aids in Reconstructive Surgery. About the Head. Presentation of a New Method, *Arch Otolaryng* **8** 531-554 (Nov) 1928. Peluse, S. A Simplified Technic for the Construction of Life Masks of Latex Rubber, *ibid* **31** 955-965 (June) 1940. Zinsser. Ein einfacher Nasenersatz, *Munchen med Wchnschr* **60** 2734 (Dec 9) 1913.

2 Brown, A M. Latex Prosthesis for Cosmetic Restoration of the Amputated Breast. *South Surgeon* **11** 181-188 (March) 1942.

The problems of these two classes of patients are different. Patients with surgical amputation of the breast require

- 1 Unilateral prosthetic correction (since generally only one breast is removed)

- 2 The restoration not only of the breast tissue but of the pectoralis muscle on the side of the operation

- 3 A prosthetic breast is constructed and designed so that when the natural breast, which usually is not perfect and often is pendulous, is lifted to its normal position the natural and the artificial breast will match as to size, shape, site and position of the nipples.

Women with congenital absence or atrophy of the breasts require

- 1 Bilateral restorations

- 2 No replacement of lost muscle

- 3 No correction of ptosis of the skin of the breasts. I make two types of breast prostheses.

- 1 Latex, hollow pneumatic prostheses molded in plaster of paris.

- 2 Sponge rubber, flexible elastic prostheses of commercial rubber molded under heat and pressure in aluminum molds.

TECHNIC FOR LATEX, HOLLOW PNEUMATIC PROSTHESES

The patient is placed in an upright position for measurements to determine the position of the artificial breast and the position of its nipple. As illustrated, a line is drawn along the length of the clavicle from the angle of Louis to the acromion process (*AB*). The measurements are made bilaterally. Another line (*AD*) is drawn vertically from the sternoclavicular notch to the hyoid cartilage. With the arms dependent at the sides a line drawn from the acromion to the olecranon process is measured and bisected. On each arm a mark is placed 1 cm below this point of bisection. A line (*CC'*) is drawn from this mark on each arm across the chest. The clavicular lines (*AB*, *AB'*) are bisected (*E*), and a line is drawn from the mid-clavicular line (*E*) of the normal side to the

nipple Where this line crosses the line CC' is the ideal location for the nipple (E') A measurement is made of the distance from the mid-sternum to the point established as the ideal site for the nipple on the normal side of the chest (DE') The same distance is measured on the side of the operation, also along the line CC' to determine the site for the artificial nipple A small object, such as a bead or a button, is glued to the skin as a landmark Now the patient is ready for the making of a negative impression Petrolatum or liquid petrolatum is lightly applied to the side of the chest having the defect The material for the negative impression may be ordinary molding plaster or one of the agar-molding compounds Three pounds (1.3 Kg) of ordinary no. 1 molding plaster is mixed with 1 pound (0.5 Kg) of potato starch

the negative impression by immersing both in hot water and separating them with a strong knife The potato starch in the negative mass tends to swell in the hot water and forces the negative mold to disintegrate The positive mold is gently cleansed and is ready for the sculpture of the new breast

Prostheses are molded with various materials Dental wax is used for some, but for a part as large as the breast modeling clay is more convenient and inexpensive The model, however, must be kept damp during the entire process of modeling Plasticine made with fine clay and olive oil is excellent and does not need to be kept damp

When the plaster is poured for the positive impression, the embedded bead or button serves as a guide to locate the position of the new

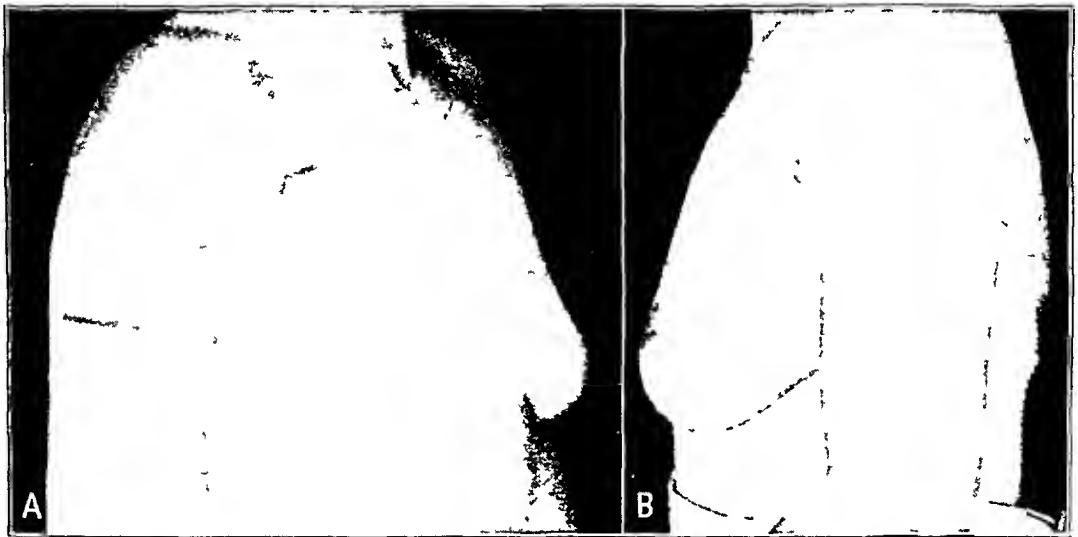


Fig 1—A, amputation of breast for carcinoma Note scar extending into axilla and loss of pectoral muscle mass B, photograph showing ptosis of remaining breast

This is mixed with water in a rubber mixing bowl and spread over half of the chest The mold should extend laterally as far as the midaxillary line and should include the shoulder and the clavicle above Thinner plaster furnishes finer detail The patient is cautioned that the plaster will become warm as it hardens and is told to breathe lightly to limit costal excursion Then the hardened plaster is removed and painted with a thin coat of petrolatum or dental separating compound

A positive reproduction of the chest can be made of various plasters Hydrocol hard dental stone hard molding plaster and rapid dental laboratory stone are all satisfactory The plaster is made into a creamy paste by mixing it with water in a rubber bowl Then it is spread thickly over the negative mold The negative is gently tapped to remove bubbles and allowed to dry The positive mold is removed from

nipple of the sculptured model A toothpick or an applicator inserted at this point serves as a marker The modeled breast is made slightly larger in all dimensions, to allow for a small amount of shrinkage in the rubber The borders of the modeled breast should be smoothed to feather edges

In the modeling of a new breast, not only must the breast be duplicated but extra mass must be provided on its lateral aspect to compensate for the loss of the pectoral muscles which have been removed surgically If the operative scar extends to the axilla, much of the scar and the consequent axillary distortion can be covered by an extension of the prosthesis

Most women use brassieres to support the breast that has not been operated on The restoration on the side of the operation is modeled not to the more or less pendulous outline of the remaining breast but with its contour

and the nipple at its artistic site. Thus when the brassiere is worn, it serves to keep the restored breast in its position and to lift the other breast to its normal place.

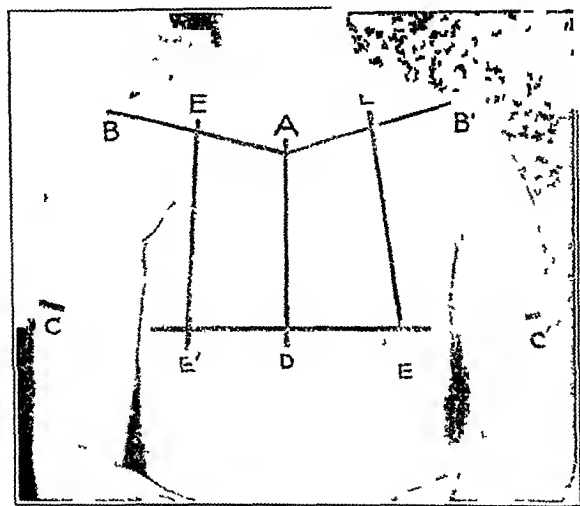


Fig 2—Method of calculating the ideal position for the nipple with the remaining nipple used as a landmark.

Once the prosthesis is modeled satisfactorily as to size, position and artistic fidelity, it is ready to have the pores of the skin reproduced, as well as the details of the nipple. To reproduce the pores of the skin, a small amount of freshly mixed plaster is poured over the skin of the remaining breast and dabbed over an area 2 or 3 cm in diameter. As it hardens a wooden applicator is inserted to serve as a handle, and when the plaster is hard it is removed and used

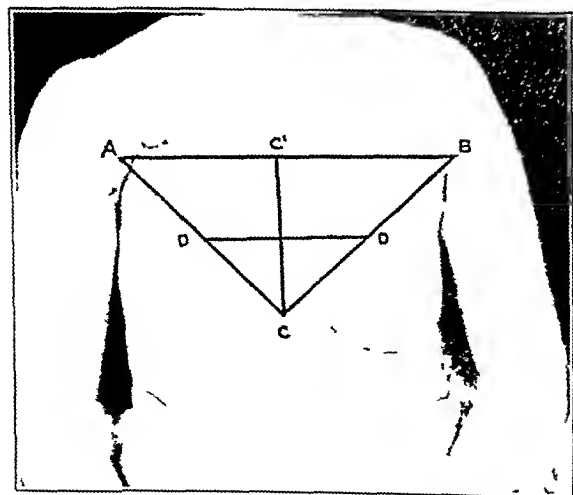


Fig 3—Method of deciding the ideal site for the nipple without regard to its original position. A triangle is drawn with the areolar cartilage and the axillas as points (ABC). It is divided vertically (CC') to establish more visible symmetry. The lines AC and BC are bisected and the points D and D' furnish the sites for the nipples.

as a tamp or an impressor to stamp the pores and the delicate skin tracery into the clay model.

The nipple may be reproduced in the same way from the normal nipple. The erectile muscles are stimulated with cold water, fast-setting hard plaster is poured over the erect nipple and after hardening is removed. If the negative impression presents undercuts, they are gently shaved away. This negative impression is pressed on the roughly modeled nipple and reproduces the pores with astonishing fidelity. To complete the positive mold, key openings are made in two or three places near the edge of the impression to insure accurate fit of the positive mold later. It is lightly coated with petrolatum, the sculptured area being avoided. This positive plaster mold will later become the bottom por-

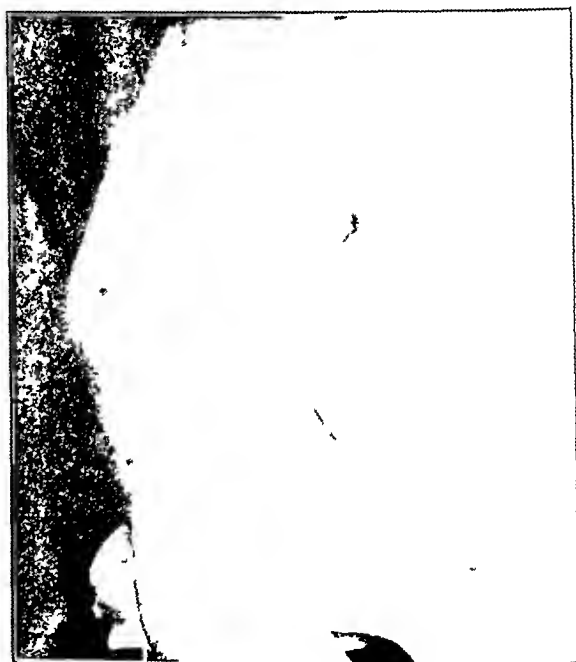


Fig 4—Latex prosthesis for unilateral restoration of the breast.

tion of a two piece mold. The positive cast bearing the sculptured breast is then covered with hard plaster. The parts of the mold are carefully pried apart and the clay washed out.

A passage for the poured rubber is then constructed. A conical opening is drilled through the bottom half of the mold, about 1 cm in diameter at the narrow end and 4 or 5 cm in diameter at the mouth. It is dug into the bottom part of the mold so that its approach is from the posterior, or hidden, side of the restoration. Now the mold is thoroughly dried, because the air content of the plaster is depended on to cure the rubber.

The type of rubber with which to cast is important. For this larger prosthesis a thick type of latex is used. Shrinkage is negligible.

and the product is firm. It may be thinned with a 28 per cent solution of ammonia.

Color is a vitally important factor in the achievement of a good prosthesis. Color added to the surface of a restoration only contributes to an artificial appearance. Color mixed with the latex before it is poured gives the restoration a nearly natural appearance with a translucence resembling that of normal skin. The colors used must be alkali-fast. Congo red, Biebrich scarlet and carmine red are suitable red dyes, burnt umber and iron oxide are satisfactory browns, and cadmium yellow and bismarck brown are also passable dyes.

Two paste colors which are stable in the presence of the ammoniacal diluent of the rubber are red CD paste and orange YOD paste³. They are made up of about 25 per cent active color and 75 per cent water and contain dispersing agents. The paste is diluted with a little ammoniated

shrinkage. If the color is not right an alteration of color is made, and a new pouring is necessary. Liquid latex is self vulcanizing; it coagulates on exposure to air. Thus plaster of paris permits the air to reach the rubber through the pores of the plaster. It also hastens coagulation by drawing the solution of ammonia off and into its own mass, the molded coagulum being left within the mold.

The edges of the prosthesis are trimmed with fine scissors and an electric burning pencil. The latter is a stylus with interchangeable points of various shapes. Seam lines may be obliterated with the heated knife edge, and irritating points on the skin side of the prosthesis may be trimmed away with it. The prosthesis may be ground smooth here and there with a high speed granite wheel, such as is used to trim vulcanite.

The prosthesis is hollow, and a few pinches of lycopodium are sprinkled or blown into the in-

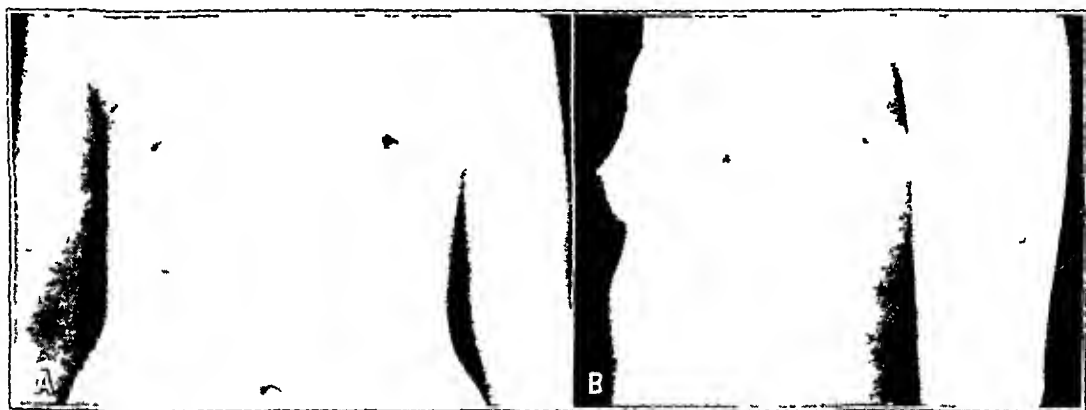


Fig 5—A and B, front and oblique views showing congenital atrophy of the breasts

distilled water to obtain more delicate tints. If color agglomerates or specks appear on the finished latex prosthesis, one may assume that the colors did not disperse easily because they were not compatible with ammonia. This, we have found, is the most common reason for flocculation.

The mold is filled with rubber and is set aside for about forty-five minutes, then the excess rubber is poured out. A layer of rubber will remain coagulated against the plaster of paris jacket. It should be about $\frac{3}{8}$ inch (10 mm) thick. If it is not thick enough the liquid latex may be poured into the mold a second time adding to its thickness. When the layer is thick enough the mold is placed in an oven at about 130 F for approximately eight hours. If an oven is not available, it may be left at room temperature for one or two days.

After drying the mold is opened and the restoration is inspected for bubbles, color and

terior to prevent adhesions within the cavity. The openings through which the rubber was poured are sealed with a thin sheet of latex. Thus the prosthesis is pneumatically sealed. The imprisoned air together with the natural elasticity of the latex rubber compound gives resiliency to the restored breast, comfort to the wearer and esthetic satisfaction.

The prosthetic breast restoration may be held in place with a brassiere. For such activities as swimming or when a brassiere cannot be worn, it may be attached with a mucilage made of styrax, gum mastic and chloroform which has been found nonirritating and convenient to use. Not only does it hold the prosthesis firmly in place but it is perspiration proof and waterproof.

TECHNIC FOR FLEXIBLE, ELASTIC SPONGE RUBBER PROSTHESES

The patient is placed in an upright position and measurements are made to determine the position of the artificial breast and the position

³ E. I. DuPont de Nemours Company, Wilmington, Del.

of the nipples as described with the preceding technic. The positive reproduction of the chest in hard plaster is also carried out in the same way. However, the entire chest must be reproduced. The new breasts are sculptured in clay slightly oversize to allow for shrinkage of the rubber. Since both breasts are being restored, much more freedom in the execution of the sculpture is permitted; no existing breast need be copied.



Fig. 6—Coloration of the prostheses by application of tinted liquid latex. The plaster hood is applied immediately after the rubber is painted on, to insure a dull finish.

The prosthetist is governed by the stature of the patient and his own artistic sense. After the sculpture is finished, the mold is completed by pouring more hydrocol over the ensemble of

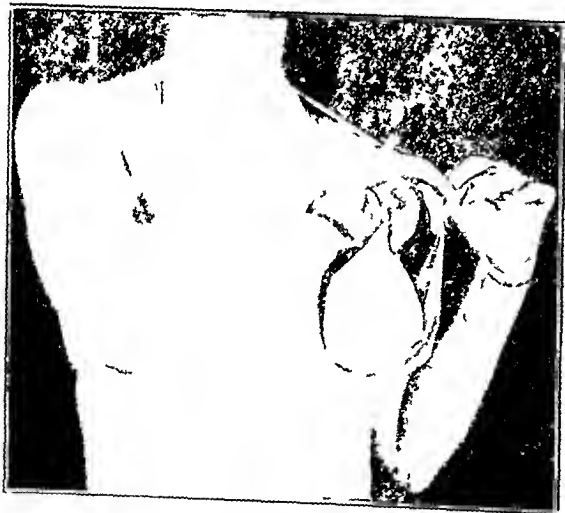


Fig. 7—Patient putting prosthesis into position.

plaster chest and sculptured breasts. After it is hardened, the mold is taken apart and the clay washed out. This process leaves a two piece mold in plaster. Unlike the first technic, no pouring channel is made; instead, the mold is cut along what would be the sternum, a die and a counter die of plaster of paris for each breast being left.

The plaster parts are now sent to the aluminum foundry for duplication in aluminum.

Standard aluminum casting technic is used. A tiny opening, about 1/32 inch (10.8 mm) in diameter, is drilled through the aluminum negative at the point of the nipple to permit the escape of air and carbon dioxide gas during the vulcanization of the rubber. It is necessary to use aluminum molds because sponge rubber prostheses are cured with heat under pressure.

The formula used for the sponge rubber prostheses is as follows:

Pale crepe rubber	180 lb (82 Kg)
Lead-free zinc oxide	10 lb (0.5 Kg)
Captan ¹	0.1875 lb (85.1 Gm)
Stearic acid	0.75 lb (340.2 Gm)
Petrolatum	60 lb (27 Kg)
Sodium bicarbonate	20 lb (0.9 Kg)
Sulfur	0.75 lb (340.2 Gm)
Glacial acetic acid	0.3125 lb (141.8 Gm)
15 per cent titanium dioxide (Diluted with Lithofoam ²)	2.5 lb (1.1 Kg)
T X red ³	5 Gm



Fig. 8—Front view with prostheses.

The amounts of the titanium dioxide and the T X red pigment are varied to furnish different shades of a basic color for the prostheses.

The various ingredients are incorporated into the mass with a milling machine. The milling machine consists essentially of two steel rollers eccentrically geared to run in the same direction at different rates of speed. The rubber mass is rolled repeatedly through the milling rollers to spread the components of the mass evenly through the batch of the pale crepe rubber.

After repeated milling, the rubber mass assumes the form of sheet rubber. A piece is cut with knife or scissors to fit the base of each mold. The mold is closed and locked under pressure.

and then heated to 300 F for approximately one hour. This heat liberates carbon dioxide in the form of countless numbers of tiny bubbles of gas, which expand the rubber and force it into every crevice of the mold. The excess gas escapes

a few more times. This rolling pressure breaks the tiny partitions between the gas bubbles and gives the prosthesis a true sponge rubber consistency. Despite the distortion caused by the rolling, the prosthesis reassumes its vulcanized



Fig 9—A and B, two oblique views with prostheses



Fig 10—Side view with prostheses

through the minute opening previously mentioned. Thus the rubber is forced into shape at the same time that it is expanded by the carbon dioxide gas and it is vulcanized in the expanded state.

After the rubber breasts are removed from the mold they are run through the milling machine

shape. Breaking the trabeculae between the bubbles makes the prosthesis softer and more resilient. Most of the gas bubbles become true spongy air bubbles.

We have found that color applied to the surface of a prosthesis gives an appearance of artificiality to the restoration. To match the

prosthesis with the skin, the rubber breast is glued back on its aluminum base, and a cap of plaster of paris is poured over it. After drying, this cap is removed.

Suitable colors are mixed with a quantity of liquid latex and painted over the prosthesis. When the colors are incorporated with the rubber which is to become a part of the prosthesis, the color coming from within the mass of the restoration simulates that of skin better than painted colors. If the liquid latex containing the color is permitted to dry of itself, it becomes glossy and enamel-like. The plaster cap is used to prevent this glossiness. Immediately after the colored rubber is applied, the cap of plaster is replaced over the prosthesis. The rubber drying against the plaster cures with a dull finish. This may be repeated until the desired color is obtained.

The breasts may be fastened in place by the following methods

- 1 They may be glued in place with a gum mastic mixture

- 2 They may be held in place with a brassiere

- 3 Both of these methods may be used simultaneously

Sponge rubber prostheses wear exceedingly well. Although their production is involved and difficult, prostheses of sponge rubber should have a definite place in restorative reconstructive surgery.

We are now attempting to make prostheses of sponge rubber to restore the contour of the calf of the leg for the atrophy following poliomyelitis. This material should be useful too for large prostheses, such as those required for esthetic correction of missing limbs.

540 North Michigan Avenue

INTRAVENOUS ADMINISTRATION OF FAT FOR NUTRITIONAL PURPOSES

EXPERIMENTAL STUDY

LUCIA J. DUNHAM, M.D.,* AND ALEXANDER BRUNSCHWIG, M.D.
CHICAGO

HISTORY AND PURPOSE

As early as 1895 Leube¹ raised the question of subcutaneous injections of fat for nutritional purposes, in connection with administration of repeated injections of camphor oil to patients with cardiac failure. Attempts were made by a number of workers² to study utilization of subcutaneously injected fat, although absorption from the sites of the injections was admittedly relatively slow. Studies on the utilization of emulsions of fats administered by vein to animals were made by Murlin and Riche in 1915,³ Nomura in 1929,^{4a} Baba in 1931⁵ and Narat in 1937^{6a, b}. It was reported that by such injections the lives of 2 starving dogs were prolonged^{6a, b} and in rabbits the iodine and saponification numbers of body fats were altered in the direction of those of the infused fats.^{4b} While it was suggested that the infused fat was deposited in the depots, adequate control studies were not reported. Under certain circumstances the respiratory quotient was lowered by intravenous administration of fat.⁵ Workers have used

dried or iodized emulsions intravenously⁷ in attempts to trace the fate of infused fat, but conclusive evidence for utilization of such fat has not been obtained.

Mansfeld in 1918⁸ reported success in intravenous administration of fat emulsions to patients as a vehicle for quinine or camphor. Other workers who have reported on the intravenous administration of fat emulsions to human beings (adults, children and infants) are Valledor (1933),⁹ Holt and co-workers (1935),¹⁰ Gordon and Levine (1935),¹¹ Myers and Blumberg (1936),¹² Narat (1938),^{6c, d} Frazer and Walsh (1939),¹³ Kramick (1940)¹⁴ and Clark and Brunschwig (1942).¹⁵ The amounts of emulsion given daily to adults have varied from 20 cc¹³ to 250 cc⁸ and the lipid concentration has ranged between 3 per cent⁸ and 10 per cent.¹⁵ Beneficial effects were reported,¹⁶ and depression of the respiratory quotient in a healthy infant was cited by Gordon and Levine¹¹ as suggestive evidence of utilization. Fat emulsions have been used to produce ketosis in the treatment of urosepsis^{6c} and to "detoxicate" bacterial toxins.¹³

Recently casein digests have been successfully administered by vein to experimental animals and to patients, in addition to the dextrose and elec-

*Fellow, Swift and Company grant
From the Department of Surgery, University of Chicago

This work was carried out under a grant from Swift and Company, Chicago

¹ Leube, W. Sitzungsber d phys-med Gesellsch zu Wurzburg, 1895, p 5

² Koehne, M., and Mendel, L. B. J. Nutrition 1 399, 1929. du Mesnil [de Rochemont], T. F. Deutsches Arch f klin Med 60 472, 1898. Mills, L. H. The Utilization of Fats and Oils Given Subcutaneously, Arch Int Med 7 694 (May) 1911. Mills, L. H., and Murlin, J. R. Proc Soc Exper Biol & Med 7 166, 1909-1910. Sommer, G. Sitzungsber d phys-med Gesellsch zu Wurzburg, 1897, p 26. Winternitz, H. Ztschr f klin Med 50 80, 1903.

³ Murlin, J. R., and Riche, J. A. Proc Soc Exper Biol & Med 13 7, 1915.

⁴ Nomura, T. (a) Tohoku J Exper Med 12 389, 1929, (b) 12 497, 1929.

⁵ Baba, T. (a) Tohoku J Exper Med 17 154, 1931, (b) 17 274, 1931.

⁶ Narat, J. K. (a) Arch i klin Chir 187 795, 1937. (b) Am J Digest Dis & Nutrition 4 107, 1937, (c) Urol & Cutan Rev 42 17, 1938, (d) J Urol 39 75 1938.

⁷ von Bodo, R., and Scheffer, L. Arch f exper Path u Pharmacol 124 326, 1927. Kimura, S. Tohoku J Exper Med 30 315, 1937. Sato, G. Tohoku J Exper Med 18 120, 1931. Saxl, P., and Donath, F. Wien Arch f inn Med 13 7, 1926.

⁸ Mansfeld, G. Wien klin Wchnschr 31 775, 1918.

⁹ Valledor, T. Arch de med d enf 36 276, 1933.

¹⁰ Holt, L. E., Jr., Tidwell, H. C., and Scott, T. I. M. J. Pediat 6 151, 1935.

¹¹ Gordon, H. H., and Levine, S. Z. Respiratory Metabolism in Infancy and in Childhood. Effect of Intravenous Infusions of Fat on Energy Exchange of Infants, Am J Dis Child 50 894 (Oct) 1935.

¹² Myers, R. J., and Blumberg, H. Proc Soc Exper Biol & Med 35 79 1936.

¹³ Frazer, A. C., and Walsh, V. G. J. Pharmacol & Exper Therap 67 476, 1939.

¹⁴ Kramick, H. G. Therap d Gegenw 81 60 1940.

¹⁵ Clark, D. E., and Brunschwig, A. Proc Soc. Exper Biol & Med 49 329, 1942.

¹⁶ Holt, Tidwell and Scott¹⁰. Kramick,¹⁴ Narat^{6c} Valledor⁹.

trolytes which have been used in routine clinical practice for many years. It seemed desirable to make further studies on the fate and possible nutritional properties of intravenously administered fat emulsions, because of the relatively high caloric value of fat and the possible indispensability of certain fatty acids for normal metabolism. Success in this direction would appear to afford further advance in the problem of supportive treatment of patients by parenteral feeding.

Studies on the lipids extracted from samples of omentum taken from dogs before and after

toxic observations were made on the liver, spleen and omentum before and after the infusions. The caloric intake, weight trends and blood and urine of the same animals were studied.

MATERIALS AND METHODS

Fat for intravenous injection was emulsified under high pressure. The emulsions were prepared by the combination of an emulsifier and a fat, in the proportion of one part of the former to two of the latter. The emulsifiers employed were commercial egg lecithin and demal 14, a mixture of polyglycerol esters manufactured by The Emulsol Corporation, Chicago (United



Fig 1—Photomicrograph ($\times 1600$) of a fresh mixture of dog's blood and a lecithin-fat emulsion to show the comparative size of red blood cells (R) and leukocytes (L) on the one hand, and fat droplets (F), on the other hand.

intravenous infusions of fat were undertaken in an attempt to identify foreign fat in the normal fat depots of the body. Foreign fat that has been fed by mouth changes the normal body fat of animals.¹⁷ If infused fat were found in the normal depots it would presumably be destined to be utilized. Parallel with studies on the lipids his-

States patent 2,022,766). The fats employed consisted of olive oil and lard oil (lowest melting point fraction of lard). A fat and an emulsifier were first stirred together in a large beaker. Gentle heating aided thorough mixture. A sufficient volume of distilled water was added to yield an emulsion that contained 4 to 75 per cent of the emulsifier and 10 to 15 per cent of the fat, by weight. Homogenization (emulsification) was obtained by passing the mixture through a dairy homogenizer at 4,500 pounds (2,025 Kg) of pressure per square inch (the homogenizer was supplied by the Cherry-Burrell Corporation, Chicago).

At first tablets of sodium chloride were added to the emulsions to afford isotonicity, but these favored break-

17 Anderson W E and Mendel L B. *J Biol Chem* 76:729 1928. Lebedeff A. *Centralbl f d med Wissen ch* 20:129 1882. Mendel, L B and Anderson W E. *Yale J Biol & Med* 3:107 1930. Munk I. *Virchow Arch path Anat* 95:407 1884.

down of the emulsions. It was then observed that 5 per cent dextrose solution was a satisfactory menstruum. Autoclaving, carried out for sterility, also resulted in some creaming of the emulsions and was not generally employed when injections into animals were made.

Microscopic examination of samples of these emulsions in a hemocytometer chamber showed that most fat droplets varied in size from a fraction of a micron to 2 microns in diameter (fig 1). Occasional droplets were as large as leukocytes, and some were 15 to 30 microns in diameter. The p_H of an emulsion of 7.5 per cent demal with 15 per cent lard oil in 5 per cent dextrose solution was 7.85, of the same type of emulsion with olive oil, 7.80, and with lecithin, 4.25.

Other emulsifiers were employed, such as soybean lecithin, "vegetable" lecithin and an anionic commercial emulsifier, which was hemolytic. All proved highly toxic.

The procedure for 13 dogs (table 1A) was (a) preliminary feeding for nine to fourteen days of commercial dog food of low fat content, 4 to 6 per cent, equivalent to 80 calories per kilogram of weight (but this was not always consumed), (b) biopsies of liver, spleen, omentum and occasionally kidney, (c) resumption of the preceding diet for four days with intravenous injections of isotonic solution of sodium chloride or infusions of 5 per cent dextrose solution in daily amounts equivalent to the volume of the fat emulsion that was injected daily after the fourth day. When the menstruum of the fat emulsion was saline solution, saline solution alone was injected in the preliminary period. The periods of infusions of fat lasted from one to thirty-six days. The quantities of emulsion infused daily were equivalent to 2 to 3 Gm of fat per kilogram of body weight. Biopsies of liver, spleen, omentum and sometimes kidney were made at the end of the period of the infusions, and from 5 dogs specimens of liver, spleen, kidney, lung and omentum were taken at necropsy (animals killed) two to eight months after the last infusion. All animals that died during the experiment were subjected to necropsy. All tissues were fixed in a 4 per cent solution of formaldehyde and stained with hematoxylin and eosin or with sudan IV in frozen sections to detect fat. As controls, 3 dogs were maintained on the diet outlined and were subjected to biopsy at proper intervals but received no fat emulsions.

EFFECT OF INFUSED FAT ON QUALITY OF DEPOT FAT (TABLE 1B)

Lipids were extracted from samples of omentum taken before and after the infusions, their iodine and saponification numbers determined and their physical states and melting points studied. It will be noted (table 1B) that after the infusions the iodine numbers rose and the saponification numbers fell in all 9 cases. The iodine numbers of lard oil (2 samples) and olive oil were definitely higher than those of the omental fat of dogs taken at control periods, and the saponification numbers were definitely lower. The same was true of the emulsifying agent demal also a lipid. Therefore the changes tabulated might at first be interpreted as proving deposition of infused foreign fat in normal fat depots. However, in spite of preliminary feedings of the commercial dog food for ten days, 3 control dogs fed on this diet twenty-eight more

days without infusions of fat showed similar shifts in the chemistry of their omental fat. In 2 dogs, A and S, fat was removed from the omentum four and a half and two and a half months after cessation of the infusions, feeding during these months having consisted of the stock laboratory diet. The quality of fat after this period resembled more closely the quality of fat before the infusions than that at the close of the twenty-one day periods of infusions and feedings of commercial dog food. We were led to conclude that changes in iodine and saponification numbers of depot fat were not appreciably affected by infusions of fat. The changes that were noted could be accounted for by the nature of the diet.

However, the physical states of the extracted fats of 4 of 9 dogs (E-1, A, 399 and 281) before and after the infusions did suggest changes in quality due to the infusions in these animals. The first samples obtained were predominantly solid at room temperatures. After the infusions the extracted samples at room temperature divided themselves clearly into fluid and solid fractions. In 1 instance the actual melting point of the fluid fraction was determined and found to be 11 to 12 C, identical with that of the infused lard oil. The physical states of the fats extracted from the control animals at the end of the experimental period were identical with those at the onset of this period, in 2 cases they were always solid and in 1 case always liquid (without solid fraction). Changes in color were noted in fats from both the control animals and those given infusions. The fats became more yellow or more orange, presumably as a result of the pigments derived from the diet of commercial dog food. Determinations of the melting point, which afforded a wide range of readings with the heterogeneous types of fat studied, were in general inconclusive. However, the melting points of the fats from dogs E-1 and A appeared definitely lower after the infusions than before, i.e. more like those of the infused fats. These physical changes presented suggestive but not conclusive evidence of changes in the quality of depot fat due to the infusions of fat in some of the animals.

HISTOLOGIC STUDIES

Biopsies before the infusions showed normal liver, spleen and omentum and omentum examined after the infusions showed no abnormalities. Tissues taken after the infusions from 13 dogs in the studies described under "Materials and Methods" are here described with others taken after infusions of fat from 11 dogs in the studies on nitrogen balance (succeeding section). Altogether of 14 dogs receiving lecithin emul-

the infusions. Individual variations in disposal or in digestion of fat appeared to be not wholly related to the emulsifying agent or to the time that had elapsed since the infusions. The lungs of dogs given demal emulsions and of animals given lecithin emulsions were alike in being normal. The picture in the sections of liver varied from an essentially normal one to one showing the presence in the parenchyma of small groups of macrophages containing fat and brown pigment giving a prussian blue reaction identical

arose as to whether this was injected fat or represented globules arising from within the cells as a result of injury incident to the infusions. It was not possible to stain fat in liver cells resulting from chloroform anesthesia by injection of sudan IV in diacetin (glyceryl diacetate) intravenously. The small amount of fat occasionally observed in normal liver cells was likewise not stained by such injections. In order to observe whether injected fat accumulated in the hepatic cells, the fat was saturated with sudan IV and

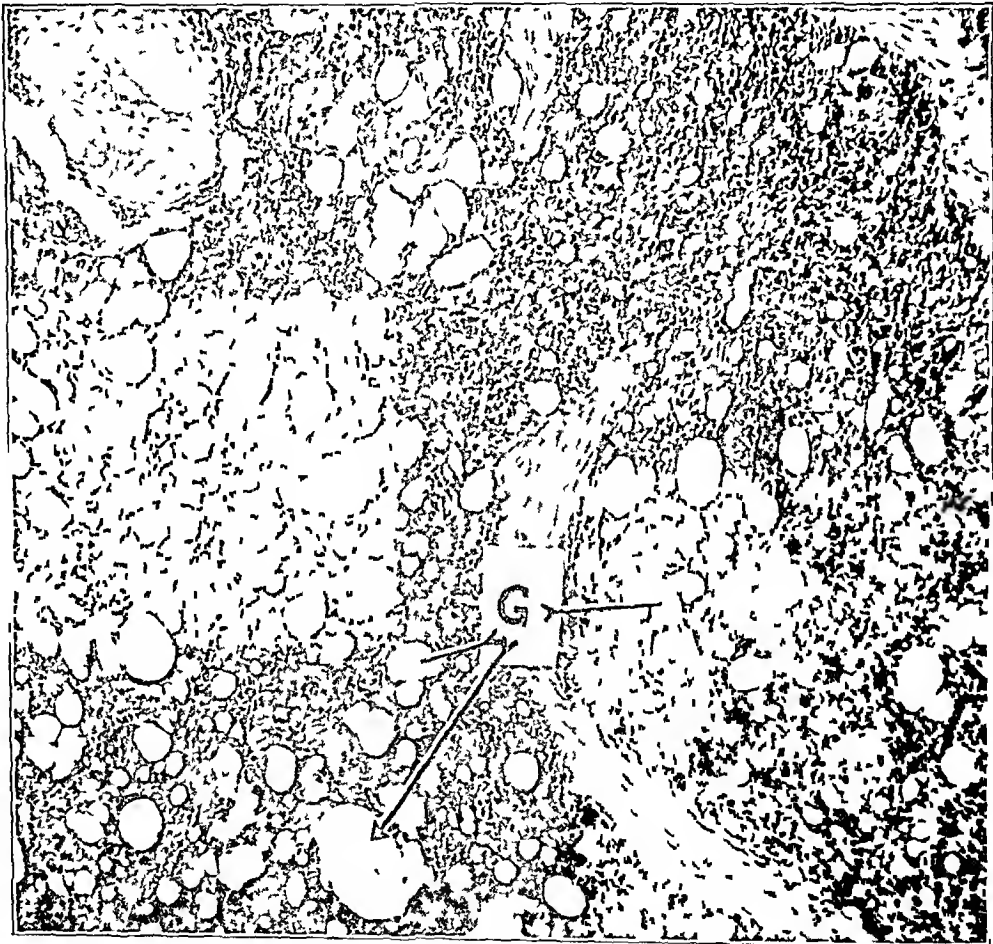


Fig 3.—Photomicrograph of a biopsy section (hematoxylin and eosin stain) taken from the spleen of dog 409 after thirty-two days of infusions of demal-fat emulsions. Large fat globules (G) are not within the macrophages but are arrested in the sinuses.

with that of hemosiderin (fig 5). Eventually both fat and hemosiderin appeared to decrease in amount and then disappear, leaving a few foreign body giant cells not lipid histiocytes (dog 499 three and a half months). In the spleen, as amounts of fat decreased, amounts of hemosiderin increased. Sections of kidney, which were for the most part normal or showed moderate amounts of fat in the glomeruli and tubules showed in 1 case (dog 544) diffuse inflammation and fibrosis.

Mention has been made before of increased fat in the liver cells after infusions. The question

the emulsion made and injected. The large globules of fat in the hepatic sinuses were stained light pink, but studies of the fat within the hepatic cells were inconclusive as to its staining, hence it was not possible to ascertain if the hepatic cell fat was exogenous or endogenous. Ten dogs were employed in this series of experiments.

THE RELATIONSHIP OF CALORIC INTAKE TO CHANGES IN WEIGHT

Of 12 dogs receiving infusions of fat and food by mouth, 4 gained weight, taking an average of

73 calories per kilogram by mouth and receiving an average of 19 calories of fat per kilogram by vein. Their gains in weight were equivalent to 3.4 to 10 per cent of the initial body weight over periods of eight to thirty-six days. Five dogs maintained a stationary weight but received an average of 57.5 calories per kilogram by mouth and 20 calories of fat per kilogram by vein. Three dogs lost weight, receiving an average of 34 calories per kilogram by mouth and 23 calories of fat per kilogram by vein. The gain or

showed a marked gain in weight (E-1) with infusions of fat when the total caloric intake was 103 calories per kilogram of weight. Weight was constant in the second course (E-2), in which a lecithin emulsion was given, and in the third course (E-3), with a demal emulsion, in which the dog showed malaise and weakness. Nine months later the animal appeared to be in vigorous health, had gained more than 3 Kg in weight on the stock diet and was not anemic. Biopsy specimens of liver and spleen showed

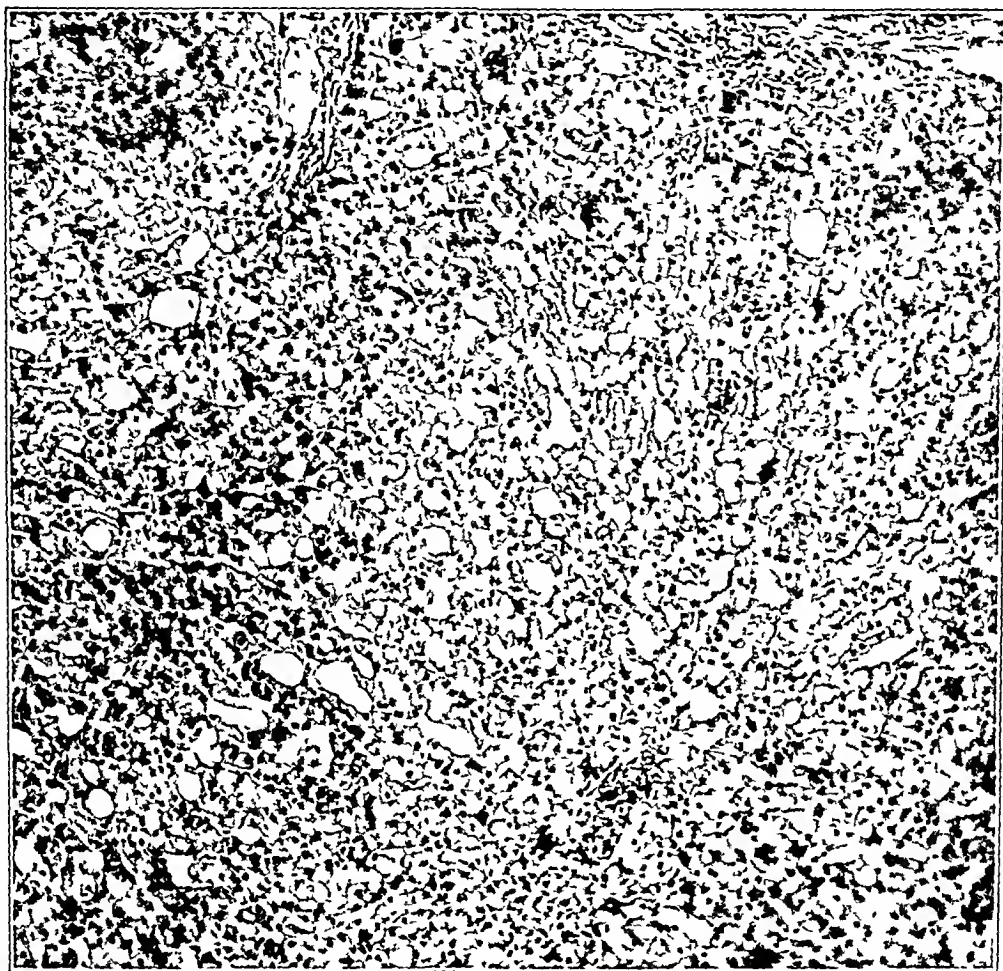


Fig. 4—Photomicrograph of a biopsy section (hematoxylin and eosin stain) taken from the liver of dog 409 after thirty-two days of infusions of demal-fat emulsions. Large fat globules appear to distend and distort the hepatic sinuses.

loss varied with the intake by mouth; the amount of fat infused having remained constant. Three control dogs maintaining caloric intakes of 65, 79 and 80 in food taken by mouth lost weight slightly. It is not possible to obtain evidence from these studies as to the extent of metabolism of the infused fat.

It will be noted that dog E (designated variously as E-1, E-2 and E-3) was given infusions of fat for three periods, a total of sixty-one days. It received a total of 1,724 Gm. of oil, exclusive of the lipids lecithin and demal, and biopsy specimens were taken four times. It

only small amounts of fat. Given infusions a fourth time in the studies on nitrogen balance (designated as dog 250 in table 2) the dog survived the infusions for only four days. There was moderate portal cirrhosis of the liver, possibly the result of repeated prolonged injury to the liver by the infusions of fat. During the second course of infusions given this dog we observed on the second day an exophthalmos of the left eye with dilated pupil and nictitating membrane covering about one third of the ball. This began to subside after five days and had disappeared eleven days later.

only disturbance we observed that might have been the result of cerebral fat embolism

BLOOD AND URINE OF DOGS GIVEN INFUSIONS

During the infusions of fat emulsions, the red blood cell count and the hematocrit reading were lowered for all dogs studied. Color indexes after the infusions did not vary significantly from those before the infusions. For 5 dogs with complete records the hematocrit readings fell to 55 to 73 per cent of the original values. The hematocrit readings of 3 control dogs fed

In most instances the blood serum was clear twenty to twenty-four hours after the infusions of fat, in some instances it was cloudy. The white blood cell count rose conspicuously, to 19,800, 26,600 and 32,600 in 3 of 6 dogs on which observations were complete. Nomura¹⁸ had observed in rabbits an early leukopenic response with subsequent leukocytosis.

No gross fat was seen in specimens of urine collected from dogs A and E over six day periods during the infusions of fat. However,

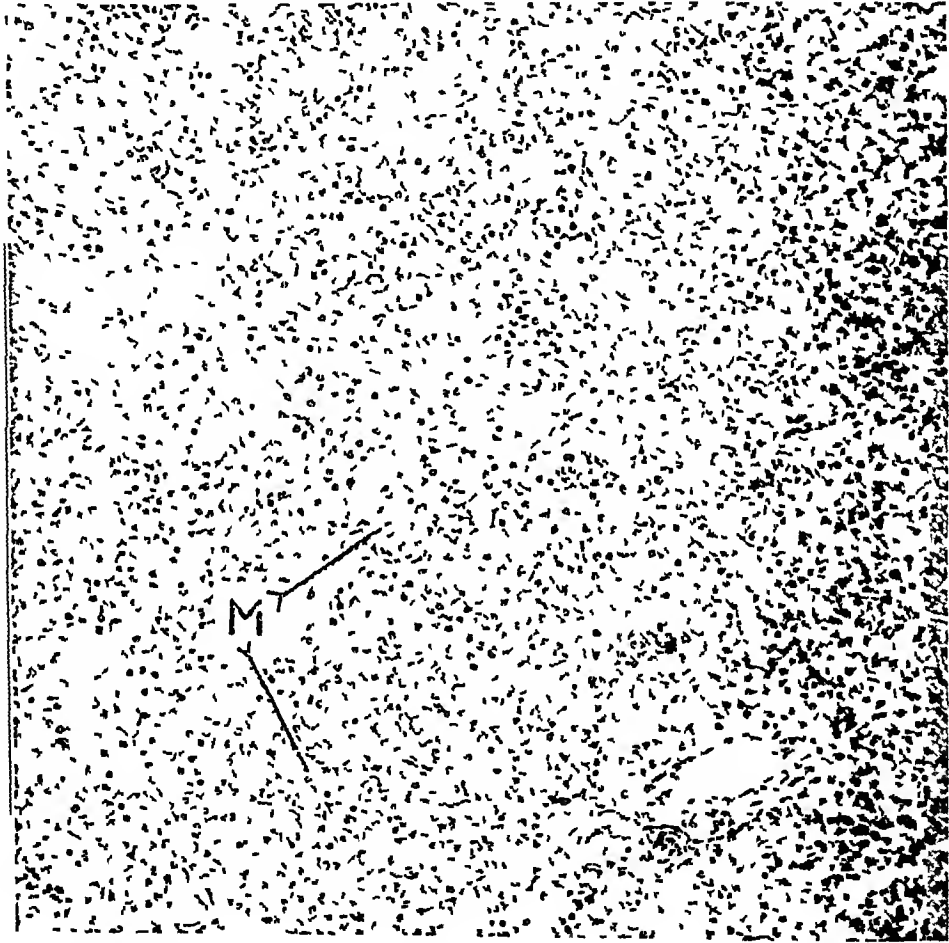


Fig 5—Photomicrograph of a biopsy section (hematoxylin and eosin stain) taken from the liver of dog 409 six months after the section shown in figure 4 was taken. Large globules of fat seen in the previous figures have now disappeared. *M* shows small foci of macrophages, some with hemosiderin and fat globules, scattered throughout the liver.

the diet of commercial dog food for comparable periods fell to 83 to 91 per cent of the original values. Improvement occurred after cessation of the infusions, hematocrit readings returning to 86 to 94 per cent of the original values during periods ranging from two and a half to six months. The infusions of fat appeared to produce severe anemia in dogs with recovery after the infusions were stopped and the dogs were returned to the stock diet. This is similar to what has been observed in the effects on the blood of high fat diets.¹⁹

ethyl ether extracts of 50 cc aliquots evaporated to dryness showed a greasy film, which was proved to be fat by staining with sudan IV. We were led to conclude that a small portion of the infused fat was excreted in the urine, as might be expected from a histologic study of the kidneys, which in some cases showed the epithelium of the convoluted tubules loaded with small fat globules.

18 Johnson V, Longini, J, and Freeman, L. W. *Science* 97: 400, 1943.

STUDIES OF NITROGEN BALANCE (TABLE 2)

Analysis of the depot fat in dogs given infusions of fat emulsions and histologic examination of their tissues had given no final proof of utilization of infused fat. Because of the nitrogen-sparing effect of fat on protein catabolism up to a point, studies were carried out to see if a reduction in excretion of nitrogen could be demonstrated as a result of the infusions of fat. Of 11 dogs used, 6 died, apparently as a result of the infusions. The others remained in good condition throughout the experiment.

The dogs were prepared by a preliminary starvation period of one week. Then 60 calories per kilogram of weight was given of the commercial dog food with a constant nitrogen content, and the urinary excretion of

TABLE 2—Excretion of Urinary Nitrogen of Dogs During Period of Infusion of Fat and Control Periods^a

Dogs	Commercial Dog Food Diet Only	Diet Plus 5% Dextrose Solution by Vein	Diet Plus Emulsion of Fat in 5% Dextrose Solution by Vein	Diet Plus 5% Dextrose Solution by Vein	Diet Plus Emulsion of Fat in 5% Dextrose Solution by Mouth
915	4.84	3.50	6.51 inc	(Died 3 days after infusions were started)	
250	9.74	8.55	9.96 inc	(Died 4 days after infusions were started)	
201	4.16	3.03	3.46 inc	(Died 4 days after infusions were started)	
543	4.52	4.01	5.02 inc	(Died 5 days after infusions were started)	
473	5.43	3.79	3.57 inc	(Died 6 days after infusions were started)	
414	13.01	8.78	9.33 inc	(Died 9 days after infusions were started)	
410	9.93	8.64	8.81	8.38	(In good health)
499	4.86	4.63	4.76	4.94	3.96
500	6.29	7.46	6.98	6.32	6.29
541	1.78	3.36	4.92	5.22	3.86
506	6.43	4.64	6.65	5.26	5.21

^a All the figures represent averages (grams of nitrogen) of values determined for forty-eight hour periods. The period of each regimen was ten days.

Nitrogen was determined. Changes in weight were followed daily but did not prove to be significant. Each dog ate his daily ration, except those becoming ill for a day or two before death. For ten days the dogs were fed only by mouth, during the next ten days a 5 per cent solution of dextrose, 20 cc per kilogram, was also given intravenously, and during a further period, of similar length, the same amounts of a 10 per cent olive oil emulsion in 5 per cent dextrose solution, instead of the dextrose solution alone, were given by vein. It was during this period that 6 dogs died, from three to nine days after the infusions were started. Five of the dogs during a fourth ten day period were again given only dextrose solution by vein, and 4 of these during a fifth

ten day period were fed a fat emulsion by stomach tube in amounts equal to those previously given by vein.

There were frequent and wide variations among the five forty-eight hour determinations of nitrogen excretion within each ten day period. When these readings were averaged it was evident that the first period of administration of dextrose lowered the nitrogen excretion of 9 of 11 dogs and that when fat in addition was given by vein the nitrogen excretion fell still further in but 1 of the 5 dogs that survived and 1 of the 6 dogs that died during this period. There was not close agreement between the quantities of nitrogen lost during the periods of infusions of dextrose before and after the period of infusions of fat. A significant period in this study appeared to be the last, in which the levels of nitrogen excretion for 4 dogs fed a fat emulsion by mouth stayed relatively stable and all averages were below the corresponding ones obtained in the period of infusions of fat. It would appear that under the conditions of the experiment fat emulsions exert more of a nitrogen-sparing effect when given by mouth than when given by vein. Hence, when fat is administered by the intravenous route as outlined there appears to be little significant and profitable utilization of it. It thus seems likely, from the lack of nitrogen-sparing effect of infused fat in the dogs and the high mortality in this experiment, that the infusions of fat exerted a deleterious effect on the dogs.

Some confirmation of the absence of nitrogen-sparing effect following infusions of fat was found in studies on a patient R. G., a man, aged 40, weighing 53.2 Kg, suffered from carcinomatosis. Nothing was taken by mouth during a nineteen day observation period when for eight days a casein digest (anigen) and dextrose were given by vein to the average equivalent of 1,052 calories per day. With this regimen the average nitrogen balance was +1.7 Gm a day. Then for eleven days a casein digest and dextrose were given to average only 852 calories per day. During this period an average of 21.6 Gm of fat (olive oil) was also infused daily. The total caloric value of the substances given by infusion equaled 1,047, which was practically identical with the calories given daily during the first period of eight days in the form of a casein digest and dextrose only. It may be argued that if the infused fat were appreciably utilized the caloric intake during the second period being the same as during the first, nitrogen balance should be

like that of the first period. However, during the second period there was a daily average loss of 0.8 Gm of nitrogen, which suggests that the infused fat was not appreciably utilized. It is true that the intake of protein was less in the period of infusions of fat than during the previous period, when it averaged 1.6 Gm per kilogram daily. During the period of infusions of fat it averaged 1.25 Gm per kilogram daily, which is still appreciably above the commonly accepted minimum, of 0.75 Gm per kilogram daily. A change from positive nitrogen balance to negative nitrogen balance of the degree cited previously would certainly not be anticipated if fat were appreciably utilized. Studies reported previously¹ on the intravenous administration of a casein digest, carbohydrate and fat to another patient showed maintenance of the patient's weight and of a positive nitrogen balance. While this patient did tolerate the infusions of fat well, it would seem in the light of these later studies that utilization of the fat did not occur. The case was reported as an example of the apparent innocuousness of intravenous injections of fat. A necropsy performed a year later on the patient afforded no evidence of permanent severe damage as a result of the infusions of fat.

COMMENT

Evidence against the utilization of emulsified fat injected intravenously is the failure to observe alteration in the quality of depot fat (iodine and saponification numbers) following the injections and the failure to observe protein-sparing effects of intravenously injected fat in 9 of 11 dogs studied. Evidence suggesting limited utilization was afforded in some studies by the alteration of melting points in depot fats in the direction of the fat infused and the presence of nitrogen-sparing effects of infused fat in dog 500 (table 2).

Infusion of fat as performed in these studies was not without danger, since 9 of 24 dogs died as a result of the infusions. It would seem likely that the cause of death was primarily mechanical interference with function of the liver, lungs and kidneys. There appeared to be no means of predicting which animals would succumb to injections of fat and which would tolerate them. The size of an animal was of no importance in this connection. The surviving dogs appeared to be in good health and to gain weight. Tissues taken when they were killed, at various intervals later, were normal or showed decreased amounts of fat that had accumulated in sites previously described.

Dogs surviving infusions of demal emulsions appeared to be as vigorous as those surviving infusions of lecithin emulsions, and 3 of the 4 dogs gaining weight had been given demal emulsions. Five dogs that died after receiving demal emulsions showed in the liver, lungs, kidneys and spleen lipid globules relatively much larger than those seen in the tissues of 4 dogs that died after receiving lecithin emulsions. It is possible that demal emulsions apparently stable *in vitro* were less stable *in vivo*, perhaps as a result of their relative instability in the presence of electrolytes. The use of synthetic emulsifying agents might well be investigated further, since if a satisfactory one should be found it would have definite advantages over lecithin, the known formula and greater ease in handling.

As stated previously, the advantages that would be afforded by successful intravenous administration of fat in addition to carbohydrate and casein digests would be in the high caloric value per unit volume and the administration of other possible essential factors in nutrition (unsaturated fatty acids). Present methods for the preparation of emulsions for such injections may be inadequate. Furthermore, little is known of the factors in the intestinal wall concerned with absorption of fat, and these factors are not operative when the fat is injected intravenously.

SUMMARY

Control dogs on a diet of commercial dog food of low fat content, 4 to 6 per cent, exhibited changes in the characteristics (iodine and saponification numbers) of the depot fat. Dogs receiving the same diet plus intravenous infusions of emulsified fat of appreciably different quality from dog fat did not exhibit sufficient differences from the control group in alteration of the iodine and saponification numbers to indicate appreciable physiologic storage of such infused fat. Changes in melting points of the depot fats in some of the animals given infusions, however, did suggest some storage of infused fat.

Protein-sparing effects were not demonstrable by intravenous injection of highly emulsified fat (except in 1 of 5 dogs), but such effects did result when comparable amounts of an emulsion were administered by mouth. This further indicated lack, or extreme limitation, of utilization of intravenously administered fat.

Histologic examination of tissues taken after infusions of fat showed increased fat in the liver, in macrophages in the spleen, in tubular epithelium of the kidneys and scattered sparsely in

capillaries and macrophages in the lungs. After administration of coarser or less stable emulsions there were large fat globules in sinuses in the liver, often in the Kupffer cells and in sinuses in the spleen, increased fat in the renal tubules and glomeruli and pulmonary capillaries loaded with fat. The foreign fat diminished with the passage of time. There was an increased amount of hemosiderin in macrophages mobilized in the

regions of accumulation of foreign fat, especially in the spleen.

The infusions of fat produced severe secondary anemia in the dogs from which they recovered after the infusions were discontinued.

The infusions of fat were probably responsible for the deaths of 9 of 24 dogs, hence such infusions are not without appreciable danger. The surviving dogs appeared to maintain good health.

OSGOOD-SCHLATTER DISEASE

EDMOND UHRY JR, MD

NEW YORK

The early modern medical literature contains references to Osgood-Schlatter disease under one name or another (see, for instance, the review by Dunlop¹) However, to Osgood² and to Schlatter³ belongs the credit for crystallizing the present day understanding of the disorder as a clinical entity In their original papers both published in 1903, Osgood and Schlatter defended the idea that the condition is a manifestation of minor trauma at the site of insertion of the patellar ligament into the tibia, in the region of its tubercle In addition, their papers contain considerable data on the anatomy and development of the structures involved The subsequent literature on the subject, while abundant, deals mainly with clinical considerations and with problems of treatment It largely lacks factual discussion of the pathologic anatomy of the condition

Apparently, the disorder results from either functional abuse of or frank insult to the region in question at the time when its developing anatomic structure withstands most poorly the stress of its function Clearly the disease is not to be included among the fractures and avulsions of the tibial tubercle resulting from severe trauma In addition to describing the pathologic picture on the basis of 23 pertinent specimens and drawing inferences from these specimens as to pathogenesis, I plan to survey (on the foundation of clinical cases from our hospital) certain more general facts relevant to the understanding of Osgood-Schlatter disease On the basis of these it will become clear that the original conception propounded by Osgood and by Schlatter, forty years ago, concerning the cause of this disease is fundamentally sound

The work reported here was done in the Laboratory Division of the Hospital for Joint Diseases while the author held the Frauenthal Orthopedic Research Fellowship prior to his entrance into the Medical Corps, U S

1 Dunlop, J The Adolescent Tibial Tubercle, Am J Orthop Surg 9 313, 1912

2 Osgood, R B Lesions of the Tibial Tubercle Occurring During Adolescence, Boston M & S J 148 114, 1903

3 Schlatter, C Verletzungen des schnabelförmigen Fortsatzes der oberen Tibiaepiphyse, Beitr z klin Chir 38 874 1903

CLINICAL CONSIDERATIONS

The clinical statistical considerations presented here are based on 79 unselected cases from the records of the Hospital for Joint Diseases⁴ The records are not complete in all these cases, but they still permit certain generalizations about the clinical picture

Table 1 groups these 79 cases by age of the subjects at the time of admission to the hospital or of registration in the outpatient department It also shows the age at time of onset of the symptoms in 55 of these 79 cases, first for both sexes together and then for each sex separately

TABLE 1—Age of Registration or Admission in 79 Cases and Age of Onset of Symptoms in 55 Cases, Charted by Year of Age

Age in Years	When first Registered or Admitted	At Onset of Symptoms	At Onset of Symptoms in Females	At Onset of Symptoms in Males
8		2	2	
9				
10	2	4	3	1
11	8	12	3	9
12	18	14		14
13	16	13	1	12
14	22	4		4
15	15	4		4
16	2			
17				
18				
19	1	1		1
20				
21	2	1		1
22	2			
23				
24	1			
Total	79	55	9	46

Specifically, table 1 shows that the onset of the symptoms was most frequently in the age period of 11 to 13 years and that symptoms most commonly reached a severity sufficient to make the patient seek medical care between the ages of 12 and 15 Furthermore, it seems clear that, as has also been found by many others, the

4 These 79 cases are by no means all of the cases of Osgood-Schlatter disease in the files of the hospital Indeed, in 1935, C J Sutro and M M Pomeranz (Osgood-Schlatter's Disease, Arch Surg 31 807 [Nov.] 1935) discussed the clinical and roentgenologic aspects of 106 cases drawn from the hospital files, and those were not all of the relevant cases even up to that time The two groups of cases overlap somewhat, but many of the 79 cases reported here date from after 1935

disease became manifest at an earlier age in the female than in the male patients, though the number of female patients forming the basis for this comparison is small. As to sex, males were definitely in the majority, there were 66 boys and only 13 girls.

In these cases the disease showed no predilection for one side of the body over the other. Specifically, the right apophysal region was the site of the lesion in 27 cases and the left in 25, while in an additional 24 cases there were bilateral lesions. (Three records failed to state which side was affected.) The group of cases previously reported from this hospital by Sutro and Pomeranz showed the same relatively even distribution. These observations are in disagreement with the general previous trend of opinion (see, for instance, Schlatter), according to which the condition occurs much more commonly on the right side than on the left.

The disorder usually appears in well developed and active subjects, who may give a history of injury, although many do not associate any such occurrence with the appearance of the disease. As the data show, the disorder may be bilateral, but is more commonly unilateral. The severity, duration and degree of incapacitation vary widely from case to case. In the majority of instances, the course of the disorder is limited by the somewhat early closure of the apophysal cartilage plate, although in a small number of cases, in which there is delay in apophysal closure, the symptoms (pain or tenderness, limitation of function, etc.) may persist well into the third decade.

Definite relevant antecedent injury was reported in a considerable proportion of the cases, but the data on this point appear to be incomplete. The trauma usually consisted of either a fall or a collision, but in not a single case had it led to gross fracture of the tibia or of any other bone. In the majority of cases pain was present on the application of hard local pressure, or even when the patient was at rest or engaged in extremely mild activity. Also in a great number of instances enlargement of the part was palpable. The histories sometimes recorded fluctuation of the swelling, increased local heat and even effusion into the knee joint. The disorder was not found objectively to have affected the stability of the knee and in the few cases in which there was limitation of motion this limitation was minor.

Review of the roentgenograms taken in our cases showed in the first place, more or less fuzziness of the border shadow of the tibial tubercle. Sometimes it also appeared that the tongue had been pried slightly upward its

prominence being increased and the space between it and the underlying tibia being abnormally wide. Occasionally, what appeared to be a shadow of a free bony fragment could be observed lying in the ligament above and in front of the tubercle. In some instances, in which roentgenograms of serial sections were made after removal of the region en masse, the evidence of loss of local definition in the bone-cartilage or bone-ligament border shadows was even more clearly apparent. In some of them the translucent or transparent shadow of a scar could be seen interposed between the bulk of the osseous apophysis and a small shadow of a flake of bone, actually avulsed forward in the process of separation. The general softness of the normal roentgen shadow of the growth zone (posterior surface of the apophysal plate) tended to obscure the changes when they occurred in that region.

The various routine clinical laboratory examinations yielded no pertinent information so far as the local lesion was concerned.

ANATOMIC CONSIDERATIONS

Before consideration of the pathologic changes in cases of Osgood-Schlatter disease, a few orienting remarks on the anatomic features and development of this region seem appropriate.

The tibial tubercle develops from a tongue of cartilage growing (at some time in early childhood) from the upper tibial epiphysis over the anterior face of the tibial metaphysis. In this cartilaginous tongue an ossification center develops, which is usually single, though it may be multiple and otherwise irregular. The ages cited for the appearance of the ossification center for the tubercle range between 8 and 15 years, but, probably, no such range exists in fact. Indeed, it seems that in most instances the ossification center appears at just about 11 years. Union of the apophysis with the epiphysis occurs a few months after the appearance of the apophysal ossification center. By about the fourteenth year of life, the apophysis presents itself roentgenographically as a sort of beak or tongue. Fusion of the beak with the shaft of the tibia frequently lags behind union of the remainder of the upper epiphysal complex of the tibia with the shaft. In the majority of instances, the beak unites with the shaft at the age of 18 years. It may unite somewhat before that age, but normally the union is rarely delayed beyond the age of 19.

During the formative stage and before fusion with the shaft of the tibia the tibial apophysis is separated from the tibial shaft by an apophysal cartilage plate. At the anterior end of this plate the patellar ligament is invaginated between the apophysal beak and the tibia for a

millimeter or two. The attachment of the ligament to the apophysis is characterized by investment of the bone by heavy ligamentous collagenous fibers, which interlock with those of the bony matrix of the part. (Occasionally one finds calcification of the ligamentous fibers at the bony junction without formation of new bone.)

The attachment of the patellar retinacula to the oblique ridges of the tibia, which curve upward and backward on either side, extending from the tubercle to the condyles, was described by Terry⁵ as follows. The lateral and medial patellar retinacula have central portions attached to the patella and arising from the rectus tendon. These pass over into the patellar ligament. The two thinner, less axial portions attach to the tibia along the oblique ridges as far from the midline as the site of attachment of the medial and lateral collateral ligaments. The patellar ligament, a continuation of the central part of the quadriceps tendon below the patella, is attached to the tibial tubercle and the upper part of the tibial crest in a somewhat oblique fashion, as the attachment is longer on the lateral side. Medially and laterally, from the sagittal plane of the tibia on either side, this ligament is continuous with the retinacula.

It is important to note that the collateral attachments of the patellar complex are able to preserve the greater part of the extension power of the knee, even though the attachment of the patellar ligament to the tibial tubercle has been invalidated. Indeed in the event of complete separation in that region, upward displacement of the patellar insertion or of any avulsed fragments of bone is sharply limited. Osgood demonstrated the efficiency of the patellar collaterals and stated that the separation of the tibial tubercle fragment from the tibia in the cadaver, in which transection had been undertaken, was only $\frac{1}{4}$ inch (0.6 cm) and that extension at the knee was not impaired.

PATHOLOGIC CHANGES

This part of the study is based, as noted, on examination of 23 adequate specimens⁶ taken from 20 subjects. From the notes dictated at the time of operation in these cases, I gathered that in general the area of the tibial tubercle appeared injected and there was increased vascu-

larity of the overlying soft tissues. Furthermore, in some cases, there was increased mobility of the tubercle, since when the latter was firmly grasped, the tongue could be forcibly moved from side to side. There was never any evidence of true fragmentation of the tubercle. Occasionally a focus of intra-ligamentous ossification was found.

To some extent on the basis of gross examination, but mainly on the basis of microscopic study, it is evident that the fundamental pathologic change in Osgood-Schlatter disease is separation of two or more structures comprising the tibial tubercle complex, with the interposition of scar tissue between them. This alteration may be found on any one or more of the interfaces formed between the patellar ligament, apophysis, apophysal cartilage plate and tibial metaphysis. In none of the specimens was there any evidence that a local disease process antedated the separation. At the site or sites of separation I characteristically observed scar tissue or even callus. In addition, I occasionally noted the presence of one or more small fragments of bone in the ligament in the general vicinity of its attachment.

In 13 of the 23 specimens, the scar-callus was seen between the patellar ligament and the apophysis—that is, on the anterior face of the tibial tubercle (fig 1 *A* and *B*). In 3 others it was present on the posterior surface of the apophysal cartilage plate (fig 1 *C*). In 4 others it was in the zone of growth, at the junction between the columns of proliferating cartilage and the newly formed endochondral bone on the posterior side of the apophysal plate. In each of the remaining 3 specimens a double lesion was present. In 2 of these separation had occurred in relation to both the anterior and the posterior surface of the apophysis—that is, at the apophysal-ligamentous surface on the one hand and at the apophysis-apophysal cartilage surface on the other (fig 2 *A*). In 1 of these 3 specimens both the anterior apophysal surface and the growth zone were involved and a fracture had occurred between the tip and the rest of the beak of the apophysis, the fragments being separated by a pseudarthrosis (fig 2 *B*). In another of them there had apparently been an incomplete fracture near the very tip of the apophysis, at which site a small cystic area, resulting apparently from liquefaction of organizing hemorrhage, was seen (fig 2 *C*).

As specimen after specimen was examined, evidence accumulated that early in the evolution of the pathologic picture organization of hemorrhage had occurred. This hemorrhage had apparently been released when the interfaces between the bone and ligament or the bone and

5 Terry, in Morris, H. Human Anatomy, edited by C. M. Jackson, ed. 9, Philadelphia, P. Blakiston's Son & Co. 1933, p. 352.

6 Of these, 16 (from 14 subjects) came from the clinical series of 79 cases from the Hospital for Joint Diseases. The other 7 (from 6 subjects) came from the collection of pathologic material preserved by the late Viennese pathologist Jacob Erdheim and now housed in the laboratory of this hospital.

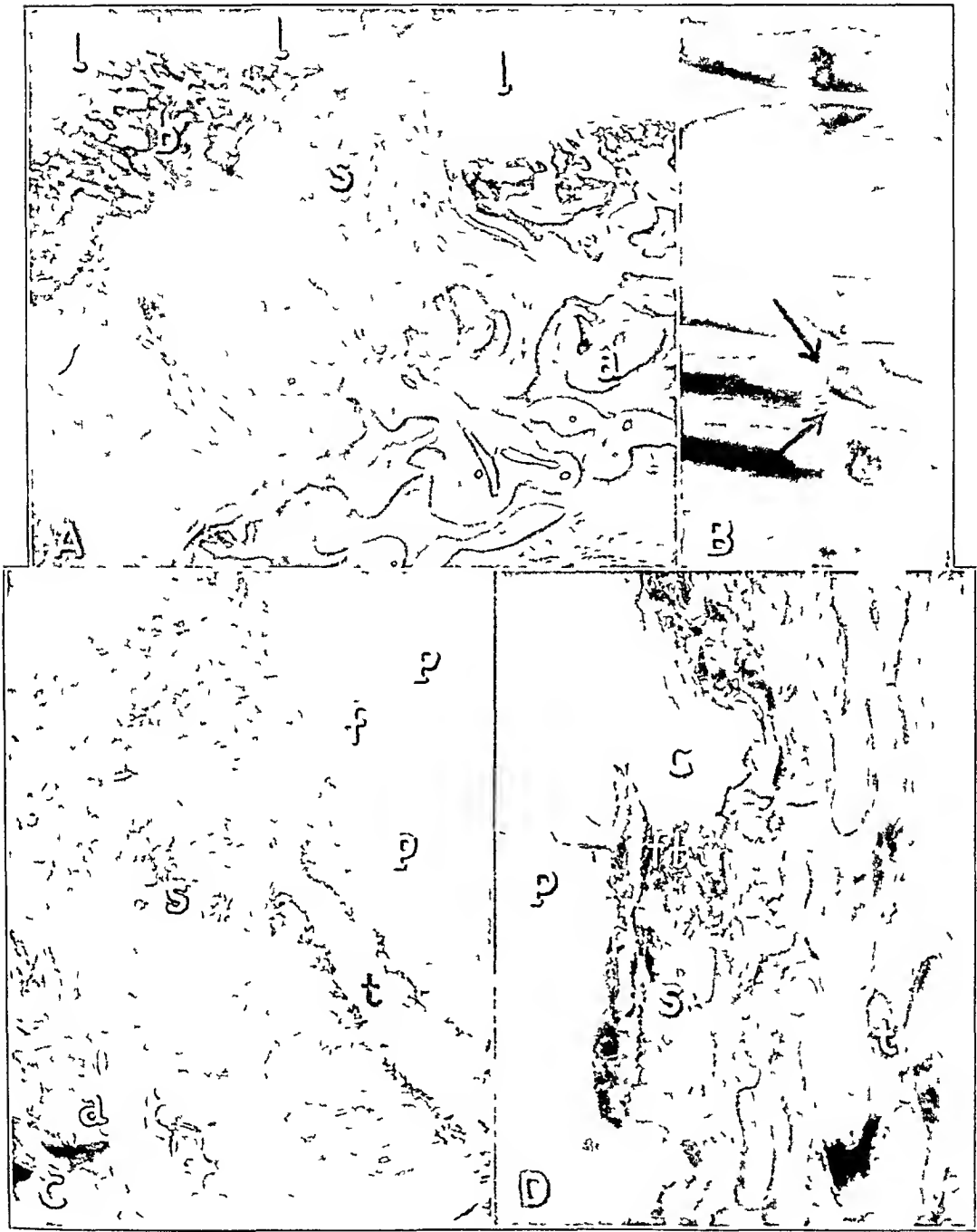


Fig 1—Scars of separation at various interfaces. *A* photomicrograph ($\times 10$) showing a scar (*s*) on the anterior face of the apophysis (*a*), note also a small fragment of bone (*b*) which has been carried forward with the ligament (*l*). The scar shows moderate vascularity and fibrous organization and the appearance of the repair tissue also suggests that this tissue did not develop in consequence of a single trauma. *B* roentgenogram of a sectioned gross specimen the piece lying between the arrows represents the slice from which the section shown in *A* was prepared. *C* photomicrograph ($\times 25$) demonstrating the conditions in another case in which the scar (*s*) lies in the interface between the apophysis (*a*) and the apophyseal plate (*p*). The scar also extends through the plate itself (*t*). A fresh separation has occurred between the scar and the plate (*t*). *D* photomicrograph ($\times 25$) showing a scar (*s*) at the growth zone of the apophyseal cartilage plate (*p*). Sparse columns of cartilage cells (*c*) indicate a slow rate of growth of bone. The metaphyseal trabeculae (*t*) are distinct. A fresh tear (*t*) indicates a recent separation.

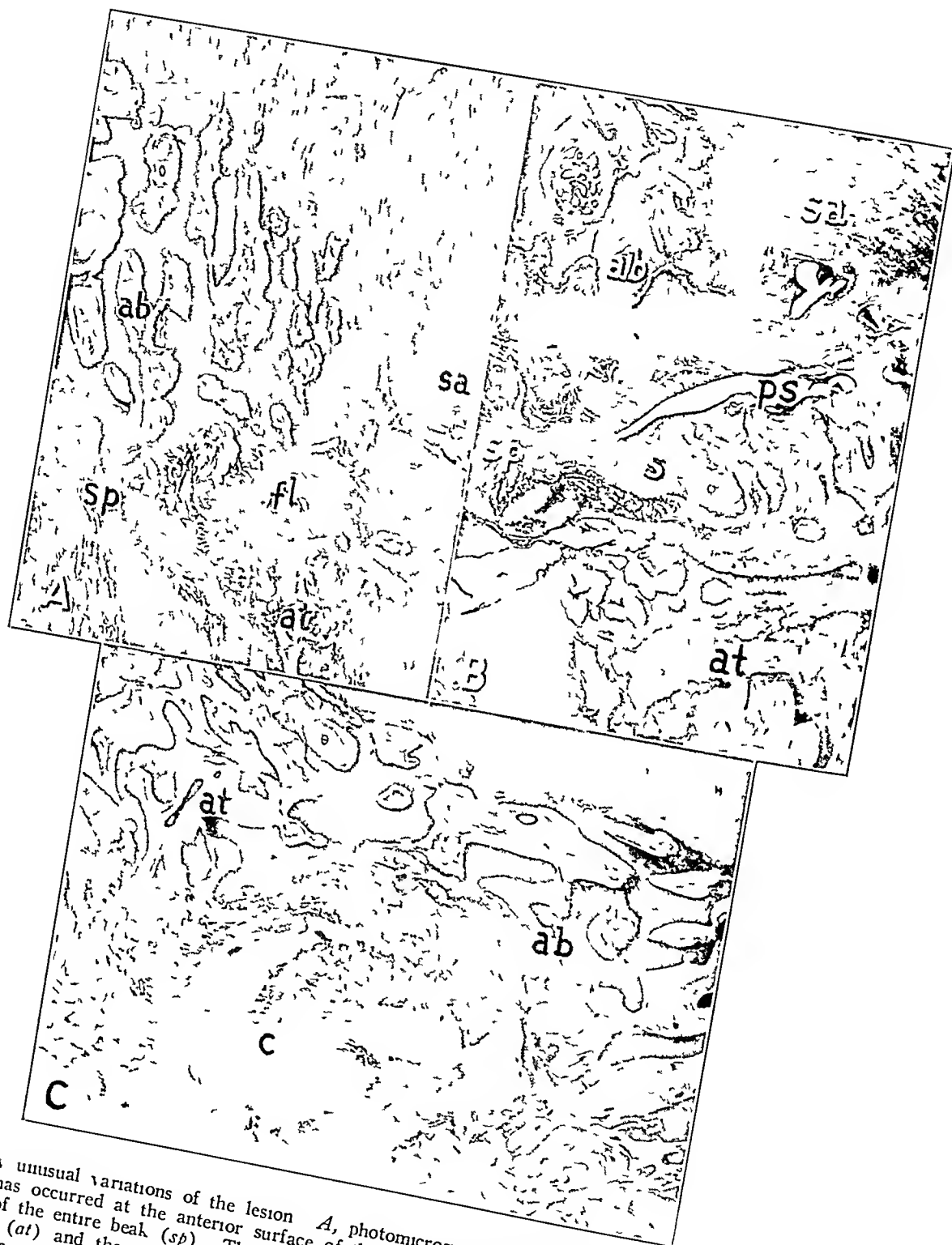


Fig 2—A few unusual variations of the lesion. *A*, photomicrograph ($\times 25$) from a case in which separation (and scar) has occurred at the anterior surface of the tip of the apophyseal beak (*sa*) and also along the posterior surface of the entire beak (*sp*). There is a fracture line (*fl*) filled in with a young scar between the apophyseal tip (*at*) and the apophyseal body (*ab*). *B*, photomicrograph ($\times 25$) showing a fracture of the tip of the apophysis, with pseudarthrosis. The tip (*at*) has broken from the body of the apophysis (*ab*), and a scar (*s*) is present between them. Scars on the anterior and posterior surfaces (*sa* and *sp*) are also shown. The pseudarthral space (*ps*) has a thin connective tissue lining, and the scar about the latter is condensed. *C*, photomicrograph ($\times 10$) showing a cystified area (*c*) between the apophyseal tip (*at*) and the apophyseal beak (*ab*) in a specimen in which the anterior surface of the apophysis is involved and an incomplete fracture of the tip has occurred.

cartilage had been disrupted. Indeed, in some specimens free hemorrhage and hemosiderin pigment were still seen in the organizing reactive connective tissue. In most of the specimens, however, at the time of examination, the organization of the hemorrhage was already further advanced and the tissue representing the scar-callus was more or less mature connective tissue of moderate cellularity and moderate to extreme vascularity (fig 3 A).

Along the line of contact between the scar and the bone, some osteoblasts, along with osteoclasts in Howship's lacunas, were observed. In many instances, fragments of necrotic bone undergoing resorption were seen in the connective tissue scar. In other specimens, trabeculae of new bone were being formed in the scar-callus, after the manner of fiber-callus (fig 3 B and C). When avulsion, particularly of the patellar ligament, carried a fragment of bone forward with it, that bone became necrotic and then underwent replacement by creeping substitution. Wherever the laceration was revealed by even a minor fracture through the bone, the osseous tissue bordering on the area was observed to be partly or completely necrotic and also undergoing creeping substitution. In the specimen presenting pseudarthrosis, an ordinary pseudarthral space had formed between condensations of the scar, which completely surrounded and lined this space. In miniature, the picture corresponded to that typical of nonunion with pseudarthrosis in larger bony structures. Furthermore, the apophysis showed fibrosis, and in some places scarring, of its marrow. Occasionally, a sparse intermingling of lymphocytes was to be seen, but there was no evidence of specific or nonspecific inflammation.

Adequate control material was examined. The material consisted of areas from normal, rachitic, tuberculous and osteomalacic tibial tubercles. In addition, control material from cases of Perthe's disease of the femoral capital epiphysis and from other instances of so-called osteochondritis (epiphysal aseptic necrosis) was examined. It should be emphasized that in none of the cases of Osgood-Schlatter disease was there anything in the anatomic picture to indicate that that disorder belongs with the so-called osteochondritides or can be related pathogenetically with any specific or nonspecific inflammatory condition.

COMMENT

If one surveys the descriptions of the pathologic changes⁷ given in the literature on Osgood-

Schlatter disease, one finds that, though the alterations have been variously interpreted, the findings themselves, as reported in these descriptions, are consistent with interpretation of the condition as a repair reaction to trauma.

The explanation of the special age of appearance of the lesion is related to the ontogenesis and the anatomic peculiarities of the tibial apophysis. Specifically, ossification in the cartilaginous precursor of this apophysis sets in at about 11 years, temporarily diminishing the resiliency of the area's response to functional demands, which happen to be particularly great in this period. After ossification of the apophysis is complete (at about 14 years), and especially after the apophysis has fused with the shaft of the tibia (at about 18 years), the region is more resistant to functional and traumatic stress. Correspondingly, in a large number of clinically and roentgenographically verified cases there are only minor lesions of brief duration. On the other hand, a considerable number of lesions persist and remain active even beyond the normal age of fusion of the apophysis with the tibia. It has been held, for instance by Brandes,⁸ that the persistence of the disorder during early adulthood is related to delay in fusion of the apophysis with the tibia in subjects in whom the condition was already present during adolescence.

der sogenannten Schlatterschen Krankheit, Ztschr f orthop Chir 48 191, 1927. von Brandis, H. J. Zur Frage der Schlatterschen Krankheit, Ztschr f orthop Chir 48 239, 1927. Cole, J. P. Study of Osgood-Schlatter's Disease, Surg, Gynec & Obst 65 55, 1937. Giuliani, G. Malattie scheletriche della crescita (Morbo del 2° metatarso di Kohler, Morbo di Osgood-Schlatter), Chir d org di movimento 17 105, 1932. Harbin, M., in Ghormley, R. K. Orthopedic Surgery, New York, Thos Nelson & Sons, 1938, p 248. Hermeto, S., Jr. A affecao de Osgood-Schlatter como anomalia de ossificacao da tuberosidade anterior da tibia, Rev Assoc paulista de med 6 61, 1935. Horbst, L. Mikroskopische Befunde bei der sogenannten Schlatter-Osgoodschen Erkrankung (apophysitis tibiae) und bei Osteochondritis des Mondbeines, Arch f orthop u Unfall-Chir 33 229, 1933. King, E. S. J. Localized Rarefying Conditions of Bone, Baltimore, William Wood & Company, 1935, pp 88, 90 and 189-203. McIlhenny, P. A. Avulsion of the Tibial Tubercle (Osgood-Schlatter's Disease), New Orleans M & S J 88 636, 1936. Quintero Fossas, J. M. Dos casos de enfermedad de Osgood-Schlatter, Rev med cubana 45 396, 1934. Sandberg, M., and Marin Moreno, N. Apofisitis tibial anterior o enfermedad de Osgood-Schlatter, Semana med 2 1917, 1932. Stracker, O. Zur Histologie der Schlatterschen Erkrankung, Ztschr f orthop Chir 58 242, 1932. Walter, H. Die Entstehung der lokalen Malacien (Osteochondritis dissecans, Perthes-, Kohler-, Schlatter'sche Krankheit und andere verwandte Prozesse), Arch f orthop u Unfall-Chir 25 557, 1927.

8 Brandes, M. Der Schlattersche Symptomenkomplex beim Erwachsenen Muench med Wochenschr 74 1830, 1927.

⁷ Anardi, T. Contributo allo studio della malattia di Osgood-Schlatter, Chir d org di movimento 12 187, 1928. Asada, T., and Kato, S. Zur Aetiology

A word should be said about fractures of the tibial tubercle in comparison with Osgood-Schlatter disease. Direct trauma and the indirect trauma of sudden, massive muscular contraction against unusual resistance do cause the tearing out of the attachment of the patellar ligament along with more or less of the underlying tubercle, with damage to the collateral structures. In some cases a part of the tibial plateau in the adult, or of the superior tibial epiphysis in younger subjects, may be torn along. The condition of fracture has been discussed in the early literature, and many of the original descriptions are included in a review by Gaudier and Bouret⁹ in 1905. This lesion is massive and is not limited to the adolescent period or by the state or existence of the apophysial plate. The differentiation of this condition from Osgood-Schlatter disease, in spite of its many gross similarities, was well understood by Osgood and by Schlatter.

Trauma is the causative factor most frequently mentioned in connection with Osgood-Schlatter disease. However, a large body of the literature, while recognizing the important role of trauma in the immediate causation of the disorder, defends the idea that the trauma acts on a tibial tubercle area which is constitutionally inferior or is already otherwise diseased. I am among those who reject the idea of these predisposing influences in this disorder and inculcate trauma alone.

The pathogenesis of Osgood-Schlatter disease on the basis of trauma alone can best be elucidated by consideration of the mechanical factors involved. The structure of the region of the tibial tubercle is laminated. The patellar ligament overlies the apophysis, which in turn is in contact with the apophysial plate, which finally, through the intermediation of its growth zone, is in contact with the tibial metaphysis. The bonds between the single elements in any such structure constitute weak points. Separation can occur cleanly at any interface between laminae, but if, locally, the bond is stronger than the substance of one of the laminae, fragments of a lamina may be carried away on separation. This

mechanism offers a background for the tearing off of flakes of bone in the specimens in which fragments of free aseptically necrotic bone were seen, usually in the patellar ligament.

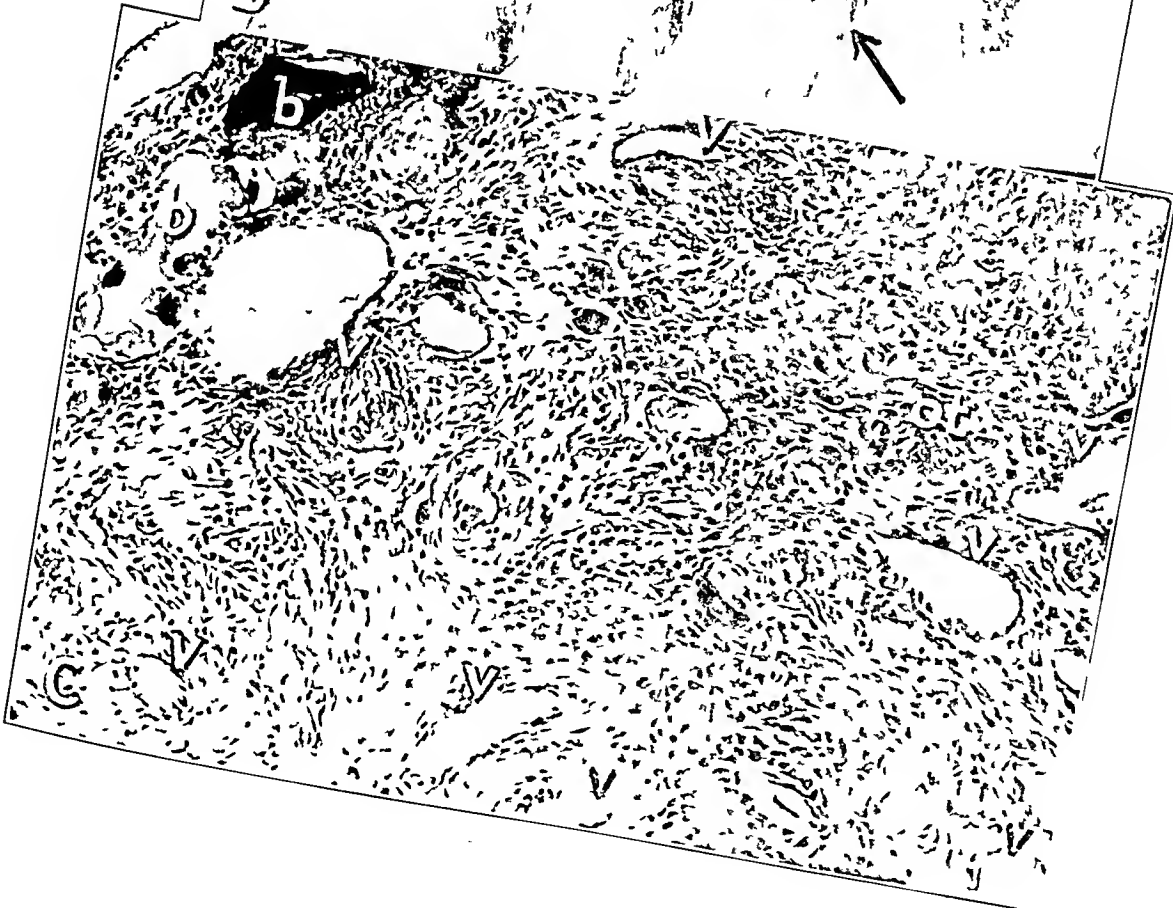
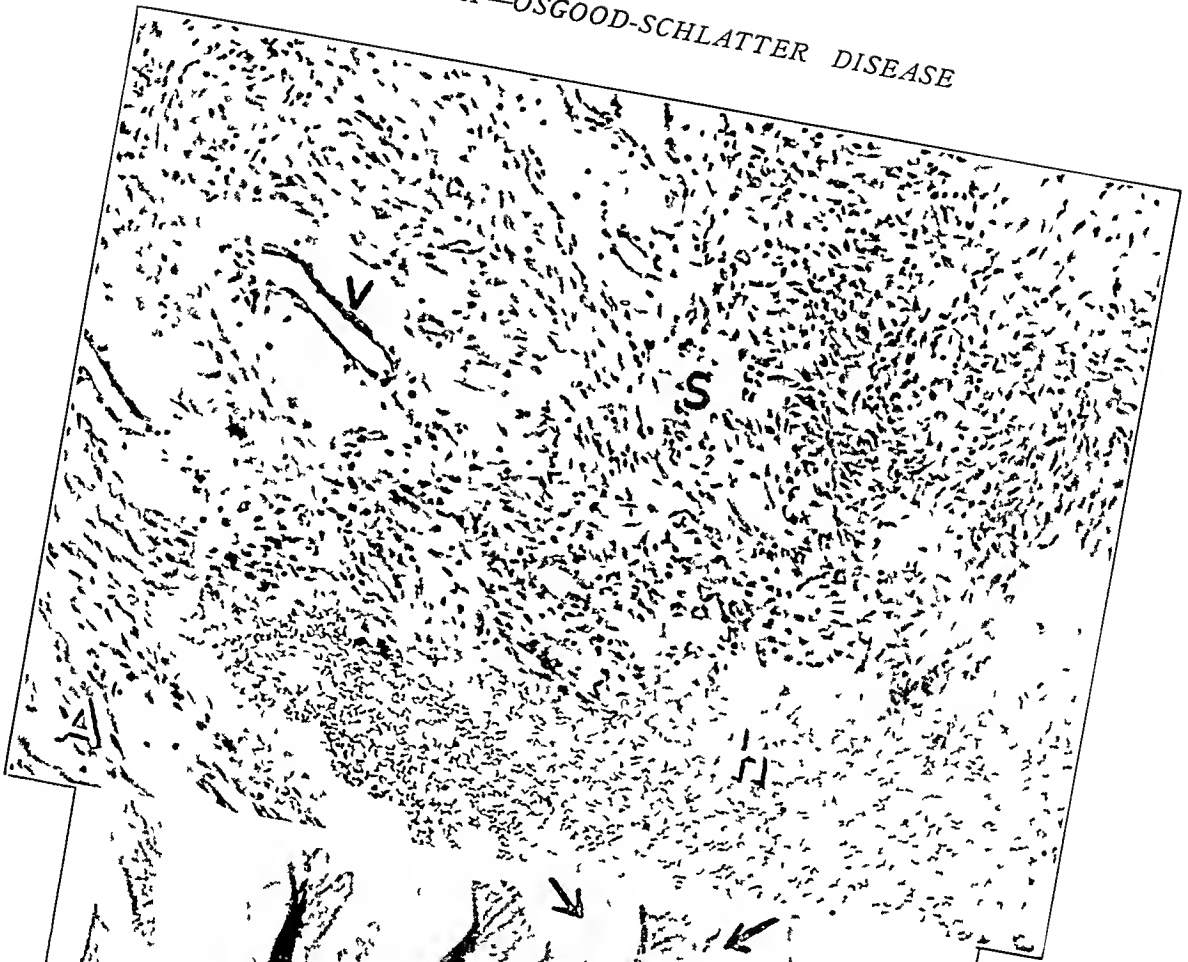
In addition, the attachment of the patellar ligament at its insertion is mechanically inadequate. The principal point of application of force, although well supported by less taut collateral structures, is extremely small, while the muscle acting, the quadriceps, is the largest in the body (Cole⁷). The pull of the muscle is always in an upward direction, in the plane of the anterior tibial crest. This direction persists, in its relation to the tibia, for any angle of flexion at the knee. This is so because the patellar insertion is located well below the axis of the hingelike motion of the knee joint and because the infrapatellar fat pad acts as a block to prevent the ligament from imposing directly on the tibial epiphysis when the quadriceps acts on the flexed knee. Furthermore, this line of force runs against the grain established by the planes of lamination of the tibial tubercle complex.

It is a familiar fact that when heavy or adherent objects are pulled along a board floor in the direction of the grain of the boards, splinters, which are the result of fractures of wood fibers, are more likely to be raised than when the stress is applied across the grain of the wood. Under the force of the quadriceps muscle there is a similar tendency for the tibial tubercle to be pried upward. The part is vulnerable to such prying action by virtue of the direction of the grain, as determined by the anteroinferior projection of the tibial tubercle and the similar direction of the planes of the interfaces involved in the tubercle complex. However, since retro-apophysial separations, such as would occur with elevation of the tubercle, are in the minority, this can be only one of the factors at work.

In view of the occurrence of the majority of separations at the anterior face of the apophysis, it may be suggested that the placement of all of the interfaces which may be involved (particularly that of the ligamentous-apophysial face) in planes very nearly parallel to the plane of the pull of the muscle favors a slipping of the parts and a beginning separation. In addition, the disparity between the size of the attachment and

9 Gaudier, and Bouret, A. O. De l'arrachement de la tuberosité antérieure du tibia, *Rev. de chir.* 32, 1905.

Fig 3—An early and a later phase in the production of the scar. *A*, photomicrograph ($\times 60$) showing a young scar (*s*) with a scattered round cell infiltration and young but well organized vascular channels (*v*). An area of hemorrhage (*h*) can be seen below. *B*, roentgenogram of a sectioned gross specimen, the piecograph ($\times 60$) showing a later phase, with early callus. Fragments of necrotic bone (*b*) can be seen under young bony resorption as are new fiber bone (*fb*) and osteoid tissue (*ot*). The blood channels (*v*) are



the force applied through it presents a constant danger of disruption

TREATMENT

The spontaneous healing that occurs in many cases after inadequate immobilization, or even no immobilization at all, indicates that many small lesions must heal without any support to the natural processes of repair. Nevertheless, it appears to me that, in general, the condition should be treated as solutions of continuity with little displacement are treated elsewhere in the skeletal system—that is, by early immobilization. Failure of this measure justifiably leads the surgeon to the use of methods indicated in cases of nonunion of true fractures, such as excision of useless fragments, freshening of apposing surfaces, reposition of displaced structures and renewed immobilization. Needling of the apophysial plate to speed its destruction and closure will not attack the more frequent site of involvement, the anterior face of the tubercle. Drilling, on the assumption that the disorder represents an osteochondritis, is unvarnished as a rule, and its use as a method of favoring new channels for vascularization and healing of a site of old nonunion is under contest at this time. In general, the impossibility of gauging the actual extent of the pathologic changes from the clinical picture in many cases clouds the evaluation of methods of treatment, because of the inclusion in the statistics on treatment of cases in which the lesions might have been

healing and might in time have subsided spontaneously

CONCLUSIONS

This study of Osgood-Schlatter disease leads me to the conclusion that the disorder develops on the basis of a minor separation of structures, one from another, in the complex comprising the tibial tubercle and patellar ligament and that the characteristic pathologic changes represent scar-callus repair at the site or sites of separation. The separation may be a clean one or may entail the inclusion of bone fragments in a softer part, as it is torn free. Any interface or combination of interfaces in the complex can be affected, but the majority of separations occur at the ligament-apophysis face, the anterior apophysial surface. Occasionally, a fracture of the very tip of the tubercle is also found, with healing or with the formation of a pseudarthrosis, in association with the processes of repair of the disruptions at the interfaces.

Inflammation (specific or nonspecific), osteochondritis, and endocrine, vascular or other specific changes are not in evidence. There seems to be no factor predisposing toward the condition other than the normal weakness of the part and its relative inadequacy to the exigencies of function and poor resistance to trauma at the time of life (usually puberty) when the disorder appears. The immediate instigating factor is consistently trauma.

Hospital for Joint Diseases

INTERSTITIAL CELL TUMORS OF THE TESTIS

REPORT OF THREE NEW CASES

EARL F NATION, M D

PASADENA

AND

HUGH A EDMONDSON, M D, AND ROY W HAMMACK, M D

LOS ANGELES

The interstitial cells of the testicle, which were first described by Leydig¹ in 1850, may rarely give rise to tumors, some of which are accompanied with endocrine changes. These cells have been regarded generally as the primary source of androgen. The study of such tumors is of interest, therefore, and may contribute to the knowledge of the normal endocrine physiology of the testis.

This paper is concerned primarily with a review of the hormonal manifestations described in the previously reported cases of interstitial cell tumor and a report of 3 new cases, in which the patients were adults, one of whom had gynecomastia. In addition, we have elaborated certain criteria for the recognition of these tumors.

LITERATURE

Several comprehensive reviews of the literature of interstitial cell neoplasia have been published recently, notably by Jemerin,² Fialho³ and Warren and Olshausen.⁴ However, these writers and others have disagreed concerning the genuineness of various reported cases, and each of them has failed to note some cases about which there can be little doubt. The reports of interstitial cell tumors which the majority of reviewers have considered authentic are listed in tables 1 and 2. The former includes those instances in which there were no associated endocrine changes, while the latter presents all cases in which the patients had such manifestations.

From the St Luke Hospital, Pasadena, the Department of Urology and the Laboratory of the Los Angeles County General Hospital and the Department of Pathology of the School of Medicine of the University of Southern California.

1 Leydig, F. Zur Anatomie der mannlicher Geschlechtsorgane und Analdrusen der Saugertiere, Ztschr f wissenschaft Zool 2 1, 1850.

2 Jemerin, E. E. Hyperplasia and Neoplasia of the Interstitial Cells of the Testicle, Arch Surg 35 967 (Nov) 1937.

3 Fialho, A. Sobre un caso de tumor de celulas de Leydig, Rev brasil de cir 10 53, 1941.

4 Warren, S., and Olshausen, K. W. Interstitial Cell Growth of the Testicle, Am J Path 19 307, 1943.

In addition to the tabulated cases of interstitial cell tumor, 7 others have been reported, but in each instance either there are insufficient data for definite classification or the original report is not available.⁵ Several other authors who have reported testicular tumors believed to be of interstitial cell origin are now thought to have been mistaken.⁶ In none of these doubt-

TABLE 1—Reports of Patients with Interstitial Cell Tumors with No Associated Endocrine Disturbances

Author	Year of Report	Age of Patient, Yr	Benign or Malignant
Chevassu Thesis, Paris, no 193, 1906	1906	27	Benign
Kaufmann Verhandl d deutsch path Gesellsch 11 237, 1907	1907	30	Benign
Kaufmann Deutsche med Wchnschr 34: 803, 1908	1908	34	Benign
Masson and Sencert ⁸	1923	62	Malignant
de Josselin de Jong ¹¹	1926	42	Malignant
Pana Urol & Cutan Rev 35 561, 1931	1931	16	Benign
Rigoletti Arch per le sc med 61 557, 1936	1936	20	Benign
Jemerin ²	1937	35	Benign
Braun Virchows Arch f path Anat 304: 106, 1939	1939	45	Benign
Fialho ³	1941	44	Benign
Masson ⁹ Venning ¹⁰	1942	32	Malignant
Warren and Olshausen ⁴	1943	30	Benign
Bonser and Hawksley, ⁷ case 1	1943	49	Benign
Bonser and Hawksley, ⁷ case 2	1943	31	Benign
Sharnoff and Lisa ¹²	1943	67	Malignant
Nation, Edmondson and Hammack case 1	1944	34	Benign
Nation, Edmondson and Hammack case 3	1944	82	Malignant

5 Peppere. Ghiandole a secrezione interna, in Foa, P. Trattato di anatomia patologica, Turin, Union tipografico-editrice torinese, 1922, vol 8, p 266. Slanina, P. Vzachny nador varlette slozeny z bunek interstitialnich, Casop lek. česk 69 935, 1930. Ciceri, C. Tumors of the Testicle, abstracted, Urol & Cutan Rev 37 648, 1933. Pitroff-Szabo, B. Die bosartigen Hodengeschwulste, Ztschr f Urol 31 823, 1937. Dehtala, cited by Fialho³. Schaany, cited by Fialho³. Ogata and Kaneko, cited by Fialho³.

6 Waldeyer, W. Die Entwicklung der Carcinome, Virchows Arch f path Anat 55 67, 1872. Hansemann D. Ueber die sogenannten Zwischenzellen des Hodens und deren Bedeutung bei pathologischen Veränderungen, ibid 142 538, 1895. Durch, H. Ueber die Zwischenzellenhyperplasie des Hodens, Verhandl d

(Footnote continued on next page)

ful or unacceptable cases did the patient have any reported hormonal changes

As will be seen in table 1, the youngest patient not having hormonal disturbances was 16 years of age (this tumor was found incidentally, at autopsy) and the oldest was 82. Ten of these 16 adult patients (63 per cent) were between 30 and 45 years of age. Five (19 per cent) of the tumors were definitely malignant. Bonser and Hawksley⁷ reported 2 tumors which they considered malignant, however, we believe that they should be classed with the benign tumors. Metastases appeared in the patient described by Masson and Sencert⁸ after four years and in the

in an undescended testis of an internally masculine pseudohermaphrodite. Some doubt has been expressed about the true nature of this tumor because of the extensive necrosis present. No metastases from the testicular tumor were found in the patient described by Sharnoff and Lisa.¹² The fifth malignant tumor is reported in our case 3.

Of the patients who had endocrine disturbances (table 2), the oldest was 42 and the youngest 5 years of age. All of the tumors in these patients were benign. The only endocrine change developing after puberty was gynecomastia which occurred in 3 patients.

TABLE 2—Reports of Patients with Interstitial Cell Tumors and Endocrine Disturbances

Author	Year of Report	Age of Patient, yr	Tumor		Endocrine Disturbances	Effect of Orchidotomy
			Benign or Malignant	Duration, yr		
Sacchi Riv. sper. di freniat. 21 149 1895	1895	9	Benign	4	Puberty at the age of 5½ years; hair on body and face, and erotic manifestations	All changes regressed except hair on lip and skeletal and muscular development
Monastchkin Ztschr. f. Urol. 20 8, 1926	1926	30	Benign	8	Bilateral gynecomastia, and atrophy of the uninvolved testis	Right orchidectomy and mastectomy followed by regression of left breast and enlargement of testis
Rowlands and Nicholson Guy's Hosp. Rep. 79 401, 1929	1929	9	Benign	3	Precocious bodily and sexual development	No regression
Stewart, Bell and Roehlke Am. J. Cancer 26 144, 1936	1936	5	Benign	1	Precocious growth of genitalia and pubic hair	All changes regressed
Budd Am. J. Path. 13 680, 1937	1937	42	Benign	½	Bilateral gynecomastia	Regression
Hunt and Budd J. Urol. 42 1242 1939	1939					
Somerford ¹⁴	1941	11	Benign	6	Macrogonitosomia	No regression after 18 months
Huffman J. Urol. 45 692, 1941	1941	6	Benign	2	Growth of genitalia, breasts and pubic hair	Genitalia smaller, no regression of pubic hair or breasts
Werner and others J. Clin. Endocrinol. 2 227 1942	1942	6	Benign	1	Precocious sexual, bodily and skeletal development	Beginning regression 3½ months after orchidectomy
Nation, Edmondson and Hammack case 2	1944	30	Benign	2	Bilateral gynecomastia	No regression after 3 years

patient described by Masson⁹ and Venning¹⁰ after nine years. The malignant interstitial cell tumor reported by de Josselin de Jong¹¹ occurred

deutsch. path. Gesellsch. 11 130, 1907. Stoppato, Ueber Zwischenzellentumoren des Hodens, Beitr. z. path. Anat. u. z. allg. Path. 50 113, 1911. Villata, G. Di un tumore del testicolo di grandi cellule rotonde e di tessuto interstiziale. Arch. per le sc. med. 52 28 1928.

7 Bonser, G. M. and Hawksley, L. M. Two Cases of Interstitial-Cell Tumour of the Human Testis, J. Path. & Bact. 55 295, 1943.

8 Masson, P. and Sencert, L. Cancer des cellules interstitielles. Bull. Assoc. franç. p. l'étude du cancer 12 555, 1923.

9 Masson, P. Tumeur maligne des cellules de Leydig. Rev. canad. de biol. 1 570, 1942.

10 Venning, E. H. Étude hormonale sur un cas de tumeur interstitielle du testicule. Rev. canad. de biol. 1 1942.

Each of the 6 tumors occurring in children was first noticed or manifested during the fourth or fifth year of life. All of the latter patients had precocious bodily and sexual development. After orchidectomy was performed the changes regressed entirely in 2 patients, partially in 2 others and not at all in the remaining 2. There was regression of gynecomastia in 2 of the adults and no regression in 1. There seemed to be no correlation between the duration of the tumor and the regression of the hormonal changes.

11 de Josselin de Jong, R. Ein Fall von Zwischenzellengeschwulst in einen ektopischen Hoden bei Pseudohermaphroditismus masculinus internus, Frankfurt Ztschr. f. Path. 34 420, 1926.

12 Sharnoff, J. G. and Lisa, J. R. Malignant Tumor of the Interstitial Cells of the Testis with Prostatic Carcinoma, J. Urol. 50 471, 1943.

REPORT OF CASES

CASE 1—P M, a 34 year old Caucasian man, a clerk, was seen on Feb 21, 1942 because of a lump in the right testis, which had been discovered by a physician one month before. There were no symptoms, and the patient's past health had been excellent. There was

in the upper pole of the right testis. The prostatic fluid was normal but contained no spermatozoa. Laboratory examinations, including roentgenographic study of the chest, contributed no significant information. With the patient under spinal anesthesia, orchidectomy on the right side was performed, at St Luke Hospital (E F N).

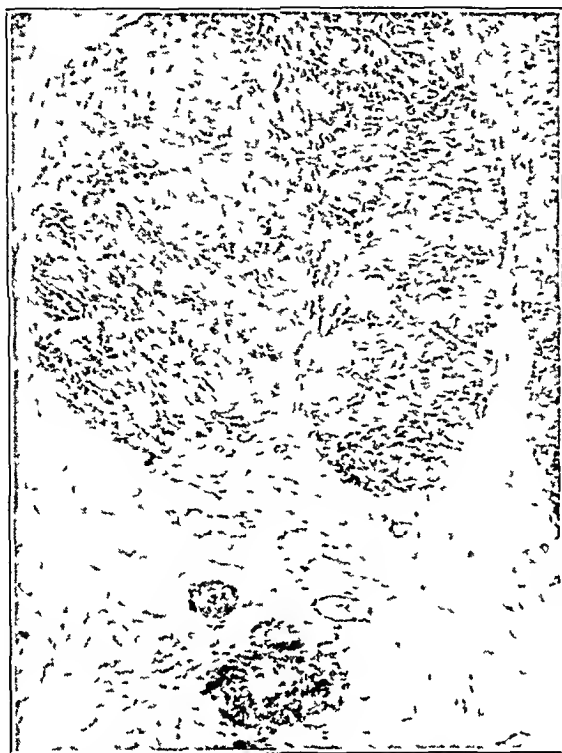


Fig 1 (case 1)—Rounded group of tumor cells showing relationship to connective tissue stroma ($\times 50$)

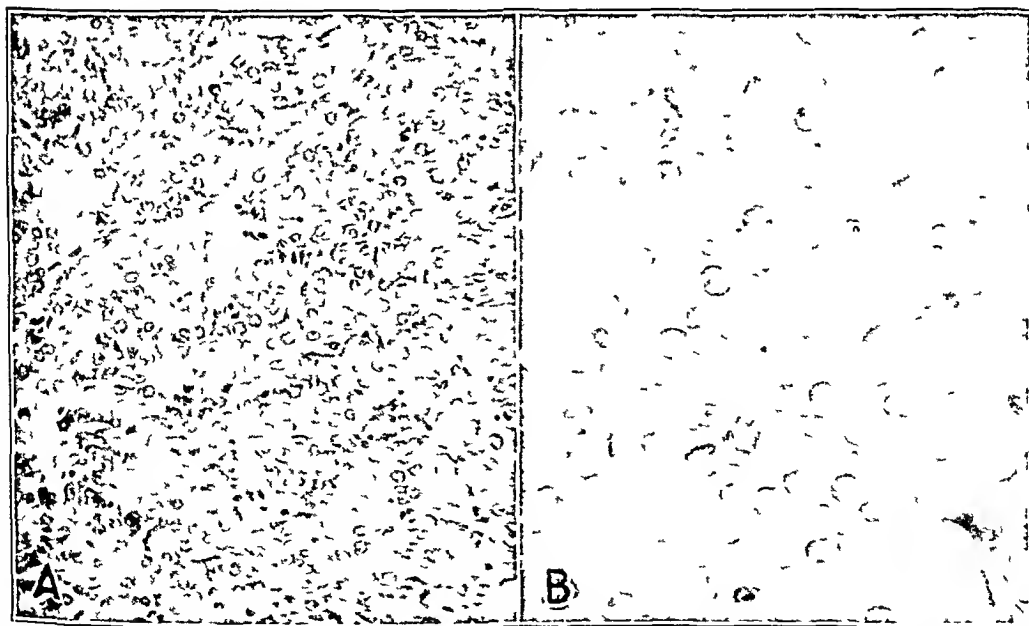


Fig 2 (case 1)—A, tumor cells with round to oval nuclei containing eccentric nucleoli ($\times 150$) B, high magnification showing cellular details, note the mitotic figure near the lower margin ($\times 450$)

no history of testicular disease or injury. The patient had been married for twelve years but had no children. Libido and potency were considered to be average. Physical examination revealed no abnormalities except a firm nontender nodular tumor, 2 cm in diameter

Six months after the operation the patient's seminal fluid contained only an occasional sperm. One and one-half years after orchidectomy the patient remained free of symptoms and exhibited no evidence of metastases.

Gross Appearance of Specimens—Specimen *A* consisted of a fairly well circumscribed mass of tumor, 1.8 to 2 cm in its greatest diameter. The external surface was slightly nodular, and there appeared to be a fairly definite capsule around the tumor. The cut surface was light brown to yellow-brown, and thin fibrous connective tissue septums were seen throughout. The brown tissue between the septums was rather soft.

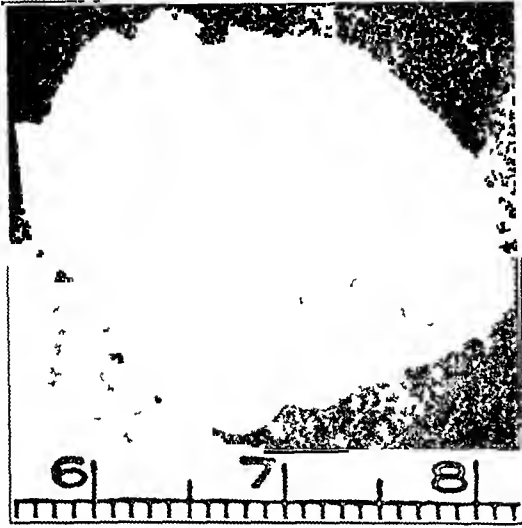


Fig 3 (case 2)—Nodular tumor of testis with fibrous capsule. (Size indicated by the metric scale.)

Specimen *B* consisted of the testicle, the epididymis and a segment of the vas deferens. The testis measured 5.5 by 3.5 by 2 cm. The surgical incision from which specimen *A* was taken appeared in the tunica albuginea. Evidence of a small amount of hemorrhage was present around this incision, but no remnants of tumor were seen. No pathologic changes were seen in the epididymis, vas deferens or vessels.

Microscopic Appearance—Sections of the tumor stained with hematoxylin and eosin disclosed it to be composed of round to irregular groups of cells resembling interstitial cells, separated by strands of relatively acellular and partially hyalinized connective tissue, in which there were a moderate number of blood vessels (fig 1). Some of these groups of tumor cells were of considerable size, and into these large groups a fine network of stroma extended. The interstitial-like cells varied to some degree in appearance; the nuclei were oval to round and moderately hyperchromatic and contained one or more nucleoli. As in normal interstitial cells, many of the nucleoli were eccentric (fig 2A).¹³ Many of the nucleoli were multiple and small and probably are best described as having a punctate appearance. Mitotic figures were rare (fig 2B). The cytoplasm of the cells was filled with fine, pink-staining granules, variable in number. In the cells of the older and more central portions of the tumor these granules were tightly packed, while in the cells of the peripheral portions they were fewer in number and the cytoplasm had a looser texture. Only an occasional cell contained

lipochrome. No Reinke crystals were seen. In some areas the cell borders were indistinguishable, while in other areas they were sharp and clearcut. Between some of the cells there were large vacuolar spaces which probably represented both areas of intercellular edema and areas from which the fat had been dissolved in preparation. In the connective tissue stroma there were small groups of tumor cells completely surrounded by connective tissue; even solitary cells remained in some areas. Attached to the capsule of the tumor were small portions of seminiferous tubules. Among the tubules were interstitial cells of Leydig, which closely resembled the cells of the tumor, except that their nuclei were not quite as large and prominent.

In a section stained with scarlet red many fine droplets of fat were visible in the cytoplasm of the tumor cells.

Multiple sections of the testis disclosed a few areas of hemorrhage around the site of the tumor but no evidence of extension of the tumor. The seminiferous tubules were uniformly atrophied, and no mature spermatozoa were seen. Most of the tubules were lined with epithelium averaging two cell layers in thickness. The interstitial cells of Leydig were normal in appearance, but their number was less than average.

CASE 2—O M, a 30 year old Caucasian, was first seen by the Mojave Clinic group, Kingman, Ariz, early in 1940. (The tissue was examined by R W H.) The patient complained of enlargement of his breasts and a testicular tumor. His right breast had begun to hypertrophy two and one-half years previously, the left testis one and one-half years before he consulted a physician and the left breast one year before he presented himself. The swollen testis had been painful for over one month.

The patient was well developed and well nourished. The breasts were several times normal size, having a definitely feminine appearance. The right breast was larger than the left. The left testis contained, in the



Fig 4 (case 3)—Testis with entire parenchyma replaced by nodular tumor. (Size indicated by the metric scale.)

lower pole, a firm, nodular tumor, approximately 2 cm in diameter. Physical examination revealed no other abnormalities, and roentgenograms contained no indications of metastases. Orchidectomy was performed on the left side.

Two and one-half years after the removal of the tumor the patient was well and had gained 30 pounds.

¹³ This feature was pointed out to us by Dr Newton Evans, Chief Pathologist of the Los Angeles County General Hospital.

(136 Kg) There was no evidence of metastases The breasts were still enlarged

Gross Appearance of Specimen—The testis had a maximum diameter of 3 cm It contained a nodular tumor, 2 cm in diameter, surrounded by a fibrous capsule, sharply separating it from the remainder of the testicle (fig 3) The tumor was firm It was gray-yellow with a few red areas scattered through its substance

Microscopic Appearance—The histologic appearance of the tumor was almost identical with that described in the report of case 1

CASE 3—S P, an 82 year old Caucasian laborer, entered the urologic outpatient department of the Los

including roentgenograms, contributed no significant information

On Oct 11, 1936, with the patient under spinal anesthesia, orchidectomy on the left side was performed (E F N) Convalescence was uneventful A Friedman test performed with urine collected two weeks after orchidectomy gave a negative result The patient did not report for roentgen therapy He was returned to another department of the hospital for examination a year later by his wife because she believed him to be psychopathic He had threatened her life and broken into her room several times The examining physician could find no evidence of insanity He did not perform a complete physical examination

The patient was then placed in a rest home under the care of a private physician Ascites developed,

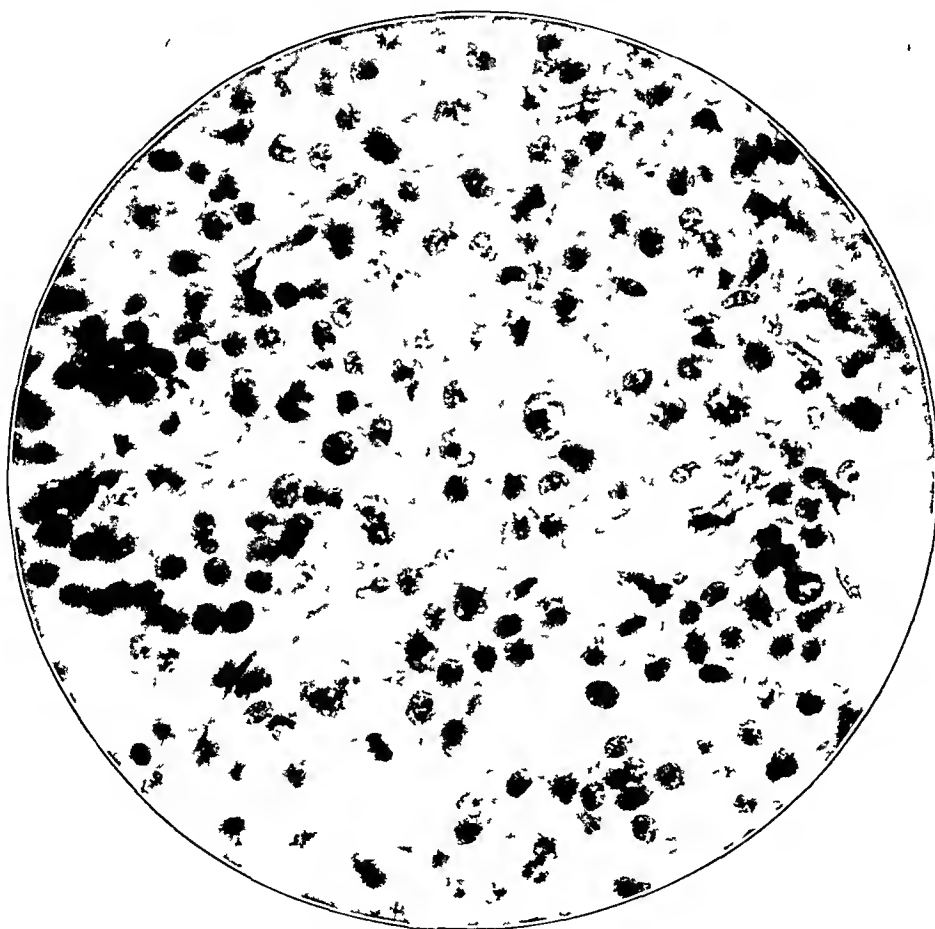


Fig 5 (case 3)—Area of anaplastic carcinoma showing many mitotic cells ($\times 450$)

Angeles County General Hospital Oct 5, 1936, complaining of a painless swelling of the left testis of two weeks' duration The past history was normal, except for typhoid fever many years before and an injury of the right hip ten years before No mention of the testes was made at physical examination in the medical outpatient department one and one-half years earlier

Physical examination revealed that the left testis was enlarged to two and one-half to three times the normal size, somewhat nodular and slightly tender The epididymis could not be isolated from the swelling The right testis was normal to palpation The following additional abnormalities were found evidence of a generalized arteriosclerosis, a moderately enlarged prostate gland, and several slightly enlarged, tender left inguinal lymph nodes The laboratory examination,

requiring repeated abdominal paracenteses, and the patient died on April 27, 1938, one and one-half years after orchidectomy, at the age of 84

Gross Appearance of Specimen—The specimen consisted of a testicle with the spermatic cord attached The testicle measured 4 by 3 by 2.5 cm There were several firm nodules on the external surface at one pole Sectioning revealed a peculiar, yellow, nodular parenchyma (fig 4) The nodules were 1 to 2 mm in diameter and apparently circumscribed by bands of fibrous tissue No normal testicular tissue was seen

Microscopic Appearance—In sections stained with hematoxylin and eosin the tumor was seen to be composed of round to oval groups of tumor cells separated by fairly thick bands of connective tissue The tumor cells resembled normal interstitial cells They had

round hyperchromatic nuclei, in which there were many mitotic figures (fig 5). Nucleoli were prominent and often eccentric. The cytoplasm varied in amount, being

In some areas the tumor cells had invaded the tunica albuginea in small groups or had grown into veins (fig 6). A few atrophic tubules were seen



Fig 6 (case 3)—Section showing growth of tumor cells in a vein ($\times 50$)

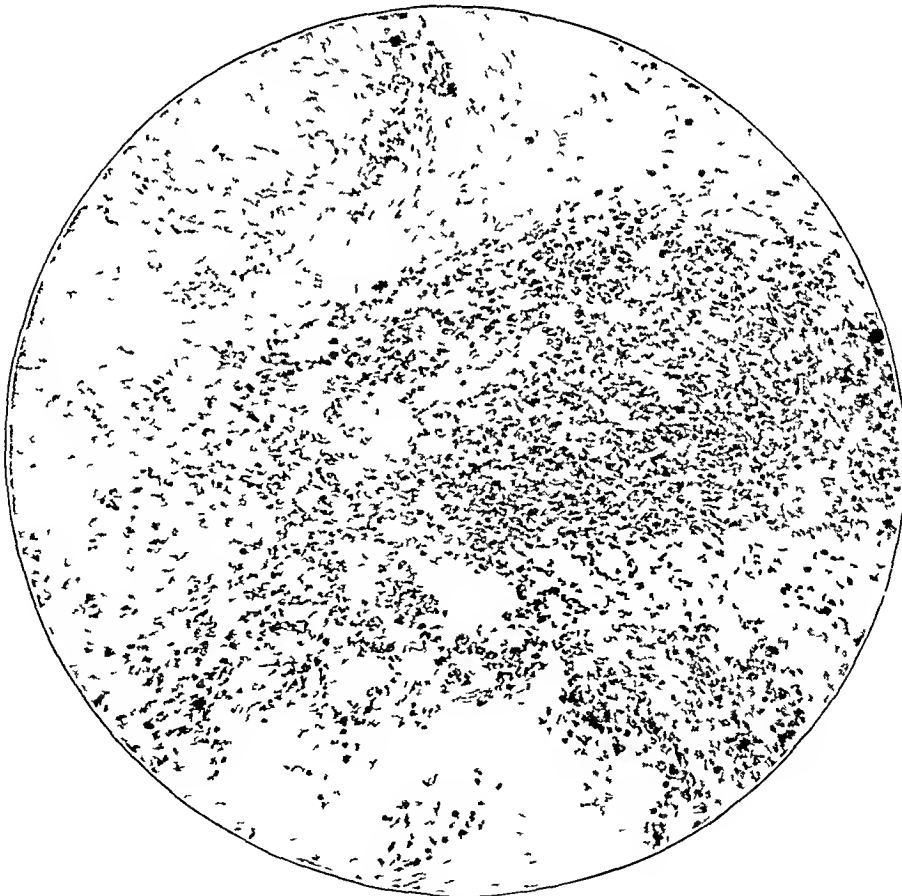


Fig 7 (case 3)—Tumor cells containing lipids (Osmic acid stain, $\times 50$)

rather scanty in some areas and profuse in others. In the latter the liver-like appearance was easily noted. Many granules of almost neutrophilic character were present.

In sections stained with osmic acid droplets of fat appeared in about one third of the tumor cells (fig 7). In portions of the tumor where growth had apparently been rapid as evidenced by the presence of

many mitoses, few or no droplets of fat were seen in the cytoplasm

COMMENT

Interstitial cell tumors of the testis have two distinctive gross characteristics. First, they are nearly all nodular. This condition is apparent on the external surface and in cross sections of the tumors and is due to the presence of nodules of interstitial cells surrounded by connective tissue. The nodules represent overdevelopment of the normal histologic structure of the groups of interstitial cells. All of the tumors reported here were grossly and microscopically nodular. The tumor reported by Somerford¹⁴ does not appear in the photomicrograph to have this characteristic relation of tumor cells to stroma. The histologic description suggests atopic adrenal tissue. It has been suggested that some of the neoplasms described as of interstitial cell origin are, in fact, tumors of atopic adrenal tissue.

The second distinctive gross characteristic of interstitial cell tumors of the testis is the color. All but 1 of the tumors, including the 3 reported here, were yellow or yellow-brown. The tumor described in the first case reported by Masson⁸ was blue-gray. As this was a malignant tumor, the cellular differentiation was perhaps not sufficient to include the formation of cytoplasmic lipids. It is the presence of lipids which causes the characteristic color of interstitial cells, and hence of these tumors. In the malignant tumor reported here (case 3) only the older, more mature parts of the tumor contained lipid (fig 7).

The microscopic appearance of interstitial cell tumors is unlike that of any other testicular neoplasm. The liver-like cells, with round to slightly oval nuclei and eccentric, punctate nucleoli are without a counterpart. These features characterize the 3 tumors described here and that of Hunt and Budd (table 2), which was available for comparison.

The hormonal changes produced by interstitial cell testicular tumors are interesting. All of the children in whom the tumors have been reported have had precocious bodily and sexual development. These are obviously androgenic phenomena. One would expect endocrine manifestations of the tumors in adults to be on the same basis.

Gynecomastia, which was reported in but 1 of the children, was present in 3 of the adults (15 per cent). Two of these patients had regression of the gynecomastia after removal of the tumor. Evidence has been adduced to indicate that androgens may cause gynecomastia. Selve

McEuen and Collip¹⁵ found development of mammary tissue and lactation in immature male and female rats after the administration of testosterone benzoate, both in the presence and in the absence of the gonads. McCullagh and Rossmiller¹⁶ noted the development of gynecomastia in 6 of 11 men treated for testicular deficiency with methyl testosterone.

The one patient with an interstitial cell tumor on whom hormone assays were performed (Masson⁹ and Venning¹⁰) did not have gynecomastia, despite having the highest level of androgen reported in any condition. Other factors, therefore, must play a part in the development of gynecomastia in some of these patients. The androgen-estrogen ratio¹⁷ may be one of these. The relationship between androgen and inhibin may be another. This has been suggested as a possible explanation of the gynecomastia found in a group of patients reported by Klinefelter, Reifenstein and Albright¹⁸. The presence of sufficient estrogen to produce gynecomastia has not been demonstrated.

Bonser¹⁹ and Bonser and Robson²⁰ produced interstitial cell neoplasia, varying from hyperplasia to the formation of malignant tumors, in mice of the Strong A strain by the injection of excessive amounts of various estrogens over a long period. Neither changes in the breasts nor other estrogenic phenomena were produced in most of these mice. The authors ascribe the absence of estrogenic phenomena to the antagonizing effect of the androgen produced by the hyperplastic interstitial cells.

This work suggests the possibility that interstitial cell tumors of the human testis could result from the formation of excessive amounts of estrogen in susceptible persons. If this hypothesis were true, the androgenic changes seen in children with tumors of this type would

15 Selye, H. McEuen, C. S., and Collip, J. B. Effect of Testosterone on the Mammary Gland, *Proc Soc Exper Biol & Med* **34** 201, 1936.

16 McCullagh, E. P., and Rossmiller, H. R. Methyl Testosterone. I. Androgenic Effects and the Production of Gynecomastia and Oligospermia, *J Clin Endocrinol* **1** 496, 1941.

17 Glass, S. J., and Bergman, H. C. Subclinical Adrenogenital Syndrome, *Endocrinology* **23** 625, 1938.

18 Klinefelter, H. F., Reifenstein, E. C., Jr., and Albright, F. Syndrome Characterized by Gynecomastia, Aspermatogenesis Without A-Leydigism, and Increased Excretion of Follicle Stimulating Hormone, *J Clin Endocrinol* **2** 615, 1942.

19 Bonser, G. M. Malignant Tumors of the Interstitial Cells of the Testis in Strong A Mice Treated with Triphenylethylene, *J Path & Bact* **54** 149, 1942.

20 Bonser, G. M., and Robson, J. M. The Effects of Prolonged Oestrogen Administration on Mice of Various Strains. Development of Tumors in the Strong A Strain, *J Path* **1940**.

14 Somerford, A. E. A Case of Interstitial Cell Tumor of the Testis in a Boy of Eleven Years, *Brit J Urol* **13** 13, 1941.

be due to excessive amounts of androgen produced by these tumors, the cells being capable of the production of larger amounts at this time of life, and the development of gynecomastia (an estrogenic change) in certain adults could be explained by the inability of their interstitial cells to produce enough androgen to antagonize the estrogen. These hypotheses are not in accord with the present understanding of the androgen-estrogen-pituitary balance and do not explain why the gynecomastia in 2 of the adults regressed after the removal of the testicular tumor. However, they indicate the necessity for extensive hormonal studies of patients with interstitial cell tumors of the testis.

The presence of a malignant interstitial cell tumor in a person dying of rapidly growing carcinoma of the prostate, as reported by Sharnoff and Lisa,¹² indicates that estrogen was not present in this patient in sufficient quantity to affect the growth of the prostatic tissue by neutralizing the androgenic effect.

Various other manifestations of these tumors have been described which could be due to excessive amounts of either androgen or estrogen. In several patients the uninvolved testis was small but grew larger after the tumor was removed. Aspermatogenesis, sterility and subnormal libido were present in several patients.

The accompaniment of interstitial cell tumors of the testis with endocrine changes, presumably androgenic, and the high level of 17-keto steroids

found by Venning¹⁰ in the urine of a patient with an interstitial cell tumor of the testis are additional evidence that the interstitial cells are the primary source of androgen in the male.

SUMMARY

Twenty-six acceptable interstitial cell tumors of the testis have been reported to date, including 3 new ones reported here. Of this number, 21 were benign and 5 malignant. One of the 3 reported here was malignant and occurred in an 82 year old man. The other 2 were in patients aged 30 and 34 years. One of the patients had gynecomastia which failed to regress after orchiectomy was performed. Each of the 6 children in whom tumors occurred had precocious bodily and sexual development. Three (15 per cent) of the adults had gynecomastia.

Interstitial cell tumors of the testis are usually nodular and yellow or yellow-brown. The microscopic picture is characteristic, there are well circumscribed groups of liver-like cells with rather small, round nuclei and many punctate nucleoli, some of which are eccentric.

It is believed that the manifestations of these tumors offer further proof that the interstitial cells of the testis are the primary source of androgen.

112 North Madison Avenue, Pasadena

School of Medicine, University of Southern California, Los Angeles

657 South Westlake Avenue, Los Angeles

SYPHILIS OF TENDON OF LONG HEAD OF BICEPS MUSCLE AND OF OLECRANON BURSA

V L SCHRAGER, MD
CHICAGO

GENERAL CONSIDERATIONS

The long head of the biceps muscle is vulnerable and receptive to both specific and nonspecific infections. This vulnerability is based on a number of factors.

Anatomic Factors—The long head of the biceps muscle is inserted into the supraglenoid tuberosity and the glenoid ligament by a long tendon (9 cm), which glides over the head of the humerus, within the capsule of the joint. It is invested with a synovial sheath, which is an evagination of the capsule, and then slides down the bicipital groove. This bursa is closed at its lower end and is 5 cm long. Codman.¹

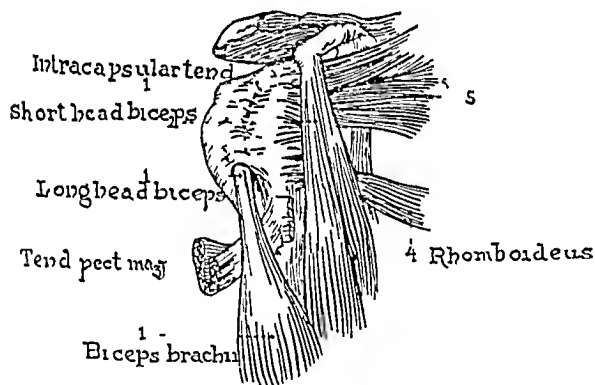


Fig 1—Long head of the biceps muscle entering the capsule of the shoulder joint (from Testut, L. *Traité d'anatomie humaine*, Paris, Gaston Doin, 1928-1931)

stated "To my mind it is more properly called a sheath, but is in fact merely an extension of the joint cavity with which it freely communicates."

Constant movement of the tendon in a rather shallow groove and relative instability of the shoulder make it possible for the tendon to be injured and to dislocate itself out of the groove. A W Meyer, of Stanford University,² dissecting 1,000 shoulders in cadavers, found 50 examples of marked dislocation of the tendon and many others of dislocation of lesser degree.

¹ Codman, E A. *The Shoulder*, Boston, T Todd Company, 1934.

² Meyer, A W. Spontaneous Dislocation and Destruction of Tendon of Long Head of Biceps Brachii, *Arch Surg* 17:493 (Sept) 1928.

Physiologic Factors—Although the tendon has several functions in the dynamics of the shoulder, it is not entirely indispensable, since the same functions are assisted, duplicated or supplemented by other muscles or tendons. Nevertheless, the physiologic assignments of the tendon are multiple, and it participates strenuously in many of the activities of the shoulder.

Pathologic Factors—The long head of the biceps muscle is a vestigial structure. Meyer² spoke of attrition of its head and of structures in its vicinity. In the course of his numerous dissections he found thinning, fraying and fibrillation. He also encountered destruction and separation of its ends with the obtainment of new tendinous attachments. He spoke of long-continued overuse in positions of abduction and external rotation. Meyer's observations were subsequently confirmed by Horwitz,³ who in the routine dissection of 150 shoulder joints in cadavers also found fraying, fibrillation and flattening of the tendon in 30 specimens. In 4 specimens complete tears were noted. Gilcreest⁴ reported 100 cases of rupture of the long head of the biceps muscle. Constant friction against deposits resulting from arthritic infections in the bicipital groove explains various degrees of damage to the tendon.

The tendon may be the seat of rheumatic infections from a focal source, it may be invaded by colon or by dysentery bacilli (J Pasteur⁵).

McKenna,⁶ speaking of tendinitis of the long head of the biceps muscle, stated in his conclusions that there are atavistic changes during the middle decades of life, consisting of avascularity, fibrillation, saponification and calcification.

³ Horwitz, M T. Lesions of Supraspinatus Tendon and Associated Structures. Investigation of Comparable Lesions in Hip Joint, *Arch Surg* 38:990 (June) 1939.

⁴ Gilcreest, E L. Rupture of Muscles and Tendons, Particularly Subcutaneous Rupture of Biceps Flexor Cubiti, *J. A. M. A.* 84:1819 (June 13) 1925.

⁵ Pasteur, J. *J. de radiol. et d'electrol.* 1:1932.

⁶ McKenna, D E. *M Times*, New York: 1940.

In April 1938, I⁷ suggested that painful or "frozen" shoulder in the absence of an actual pathologic condition within the joint or bursas is due to tendosynovitis of the long head of the biceps muscle. What was then a mere clinical conjecture has just been proved to be a fact by Lippmann.⁸ His pathologic material was obtained from 12 surgical cases of "frozen shoulder" and was appraised by Dr. Oppenheim, pathologist at the Mount Sinai Hospital of New York, who found various degrees of inflammation in all specimens.

It can thus be seen that anatomically, by virtue of its arrangement, this tendon is a somewhat handicapped one. Physiologically, the tendon is taxed beyond its physiologic assignments. Pathologically, it falls prey to various types of nonspecific and specific infections.

This is, then, the background of this vulnerable tendon, which places it in a status minoris resistentiae.

trian syphilologist, published in 1884 an extensive article on syphilis of tendons and joints. Like Verneuil, he described acute and subacute exudate in the tendon sheaths of extensor muscles of fingers, especially in women. In Germany, Schuchardt¹¹ and Holder¹² spoke of syphilis of tendons, the latter finding the condition more prevalent in muscles. In the United States, Keyes¹³ mentioned the subject and reported several cases. Hektoen and Riesman¹⁴ spoke of tendovaginitis acuta syphilitica occurring in secondary syphilis. Stokes,¹⁵ on the other hand, stated that the involvement of tendon sheaths in early syphilis is rare.

The literature on syphilis of tendons seems to have been prolific in the seventies and eighties, especially in France, sporadic thereafter and seldom mentioned in modern literature on syphilis. While it is difficult to explain the discrepancy between the thorough knowledge of the subject in the seventies and eighties and the total

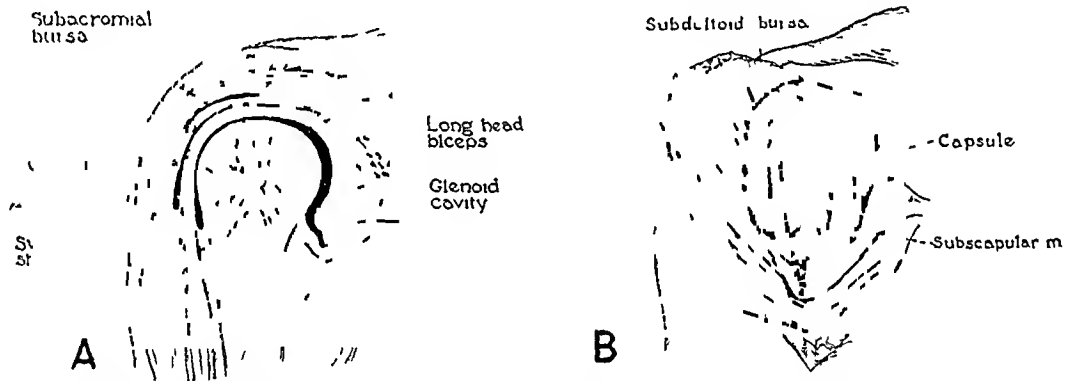


Fig 2—A shows the tendon of the long head of the biceps muscle in relation to the joint capsule and humerus, B the tendon with the synovial sheath split and reflected outward (from Callander, C. L. *Surgical Anatomy*, Philadelphia, W. B. Saunders Company, 1933).

SYPHILIS OF TENDONS AND TENDON SHEATHS

History—Verneuil⁹ stated that prior to 1868 there was no mention of syphilis of tendons in the literature. He reported 4 cases of syphilitic "subacute exudate" in the tendon sheaths of extensor muscles of fingers, all the patients were women.

The French school of syphilologists, represented by Fournier, Velpeau, Lancereaux, Verneuil, Mauriac and others, reported a number of cases of syphilis of tendons. Finger,¹⁰ Aus-

oblivion in modern times, it may be that the syphilologist of old, deprived of the advantages of serologic diagnosis, was a keener clinician. Again, modern antisyphilitic treatment has either modified or obviated the pathologic changes of syphilis.

Etiology and Diagnosis—The earliest diagnoses were established largely on therapeutic tests, some of the syphilitic tendinitis disappearing like magic on this treatment. Syphilis of tendons is seldom suspected, tendinitis being the

7 Schragar, V. L. *Surg., Gynec. & Obst.* 66:785, 1938.

8 Lippmann, R. K. Frozen Shoulder. Periarthritis, Bicipital Tenosynovitis, *Arch. Surg.* 47:283 (Sept) 1943.

9 Verneuil. *Gaz. hebdomadaire de med.* 5:609, 1869.

10 Finger, E. A. *Wien. med. Wochenschr.* 34:864, 890, 920, 944, 971, 993 and 1026, 1884. *Lehrbuch der Haut- und Geschlechtskrankheiten*, Leipzig: F. Deuticke, 1907.

11 Schuchardt, K. *Virchows Arch. f. path. Anat.* 135:394, 1894.

12 Holder. *Lehrbuch der venerischen Krankheiten*, 1909, pp. 185 and 421.

13 Keyes, E. L., Jr. *Syphilis*, New York, D. Appleton and Company, 1908.

14 Hektoen, L., and Riesman, D. *An American Text-Book of Pathology*, Philadelphia, W. B. Saunders Company, 1901.

15 Stokes, J. H. *Modern Clinical Syphilology*, Philadelphia, W. B. Saunders Company, 1934, p. 687.

prevalent diagnosis for acute conditions and ganglion or tuberculosis for chronic conditions

A history of syphilis, especially in untreated or inadequately treated patients, positive serologic reactions and characteristic scars on the forehead and the tibia are helpful in diagnosis. However, many untreated patients show a slightly positive and frequently a negative reaction.

The presence of a mass may suggest a tumor, as it did in the case to be described. However, tumors of the tendon sheaths are rare. Canavero¹⁶ estimated that there are approximately 1 or 2 cases of such growths in every 2,000 admissions to hospitals and clinics. In the combined statistics of the Brooklyn Cancer Institute, the Cumberland Hospital and the Jewish Sanatorium and Hospital for Chronic Diseases, there were only 5 cases of tumor of the tendon sheath among 1,500 admissions to the hospitals and 150,000 admissions to the clinics. Coley and Pierson¹⁷ collected 27 cases of tumor of the synovial sheath from the general literature.

Syphilitic tendinitis may be associated with painless swelling of joints, which is invariably diagnosed at first as being rheumatic or arthritic. The pain, if at all present, is more likely to be nocturnal and is often relieved by exercise. Fournier expressed the opinion that pains about the knee and elbow at the beginning of secondary syphilis are due to syphilis of tendons in the vicinity of joints. He stated that the pain at the bend of the elbow and the inability of the patient to extend the forearm are characteristic of secondary syphilis, and he designated the condition pseudorheumatism. Pains about the elbow of syphilitic origin may be referred to the tendon of the long head of the biceps.

The exudate may be either slightly painful or, more often, painless and as a rule does not affect function. There may be present thickening of the tendons and painless and movable nodules along their course. The overlying skin may either be normal or show inflammatory changes, sinuses, thickening or calcification.

Pathology—One of the characteristics of syphilitic tendinitis is the presence of nodules in the tendons. Lisfranc¹⁸ described white nodosities in tendons (*nodosites blanches*), which Lancereaux¹⁹ ascribed to syphilis. They always are a tertiary manifestation, painless and movable. Schuchardt¹¹ reported a case in which a hazelnut-

sized node in the long head of the biceps of a merchant with untreated syphilis responded well to antisyphilitic treatment. Lisfranc described "white tumor" in the achilles tendon of an opera dancer, which disappeared completely on the administration of potassium iodide.

Syphilis has a predilection for certain tendons. According to Lancereaux, thick and strong tendons are more often involved, such as those of the biceps and triceps surae muscles and the extensor muscles of fingers. Schuchardt reported syphilitic nodules in the tendon sheaths of the supinator longus, extensor carpi radialis and extensor pollicis longus muscles, all in female patients.

Many syphilologists have mentioned involvement of the tendon of the long head of the biceps muscle. Cases of such involvement have been reported by Fournier, Schuchardt and Lisfranc. Fournier stated the belief that tendosynovitis of the tendon of the long head of the biceps muscle is characteristic of secondary syphilis and that the pain, if present, is always referred to the elbow.

Lancereaux spoke of plastic exudate, infiltration and thickening, as well as of gummas. Schuchardt found thickening of the inner sheath of tendons. He also found masses of lymphocytes, which he designated as milary gummatous nodules and areas of necrosis, resembling caseous gummas of the testicle. There were present in the granulation tissue of the deeper layers of tendon sheaths giant cells with multiple nuclei, resembling those present in tuberculosis.

REPORT OF A CASE

History—I W., aged 61, retired, was a well built and well nourished man, looking a bit younger than his age. He had been in fair general health all his life. For the last twenty years, however, he had complained of pain in various joints, and he had been incapacitated for about twelve years. During that time he had had periodic large swellings in various joints, such as those of the shoulder, the wrist and the knee, which inconvenienced him because of the size of the swellings but not because of pain. He could get around well using a cane, or occasionally crutches, simply because they made walking a little easier. He consulted several physicians, who diagnosed his condition as either rheumatism or arthritis. During the last routine examination it was discovered that his blood showed a 4 plus Wassermann reaction. The attending physician gave him several injections of neoarsphenamine and bismuth. After the eighth treatment, a deep jaundice developed. The patient became alarmed, discontinued the treatment and visited the Mayo Clinic, in Rochester, Minn. There, a diagnosis of toxic hepatitis was made and he was advised never again to take a course of the treatment of syphilis. He had not had syphilitic treatment since.

When I saw the patient he stated that previously, while squeezing an apple, he had experienced a rather sharp pain in the upper

¹⁶ Canavero, M. *Polichinico (sez chir)* 41 341 (Jul.) 1934

¹⁷ Coley, B. L., and Pierson, J. C. *Surgery* 1 113, 1917

¹⁸ Lisfranc, J. *Gaz d hôp*, 1842

¹⁹ Lancereaux, E. *Traité historique et pratique de la syphilis*, Paris, J.-B. Baillière & fils, ed 2, Paris, Germer-Baillière, 1873

A couple of days later he noticed a swelling in that location, which was painless. This swelling progressed in size, and when I saw him, about a week later, he insisted that the tumor mass be removed.

Examination of the patient revealed that he had no organic disease and that he was in excellent condition for his age. There was a large swelling, elastic in character, in both knees, which were painless both to touch and pressure and on active and passive movement. The ankles were slightly swollen, there was some swelling in the left shoulder, which was the residual of a former, larger swelling. The routine laboratory tests gave normal results. As mentioned before, the original Kahn and Wassermann reactions were negative, but there was a 2 plus reaction with other methods. In the upper third of the right arm, on its anterior and lateral aspect, there was a tumor mass the shape of a large banana. It was somewhat soft, was painless and could be displaced laterally but not upward or downward. There was also a large, inflamed olecranon bursa, about the size of a large walnut, likewise painless and movable.

On the basis of the age of the patient, his reasonably good record of health, his healthy children and the fact that for a number of years he had had effusions

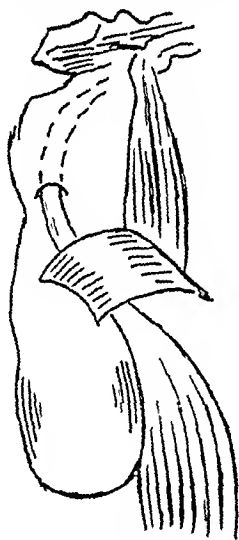


Fig 3—A tumor mass displacing the tendon and muscle laterally.

in various parts of the body, two tentative diagnoses were made: tumor of undetermined origin, or serous effusion in the tendon sheath of the long head of the biceps muscle. The olecranon bursitis was considered coincidental and not related to the tumor mass in the upper portion of the arm.

Operation and Findings—With the area under anesthesia induced with solution of procaine hydrochloride, an incision was made in the upper third of the arm, laterally to the midline. The tumor mass was about 3 inches (75 cm) in length and about 1½ inches (38 cm) in width. It was located in the tendon sheath of the long head of the biceps muscle and, by its size, displaced the muscle laterally and internally.

The mass had a thin capsule of connective tissue. It was movable laterally, but it was attached to the deeper structures and could not be moved upward or downward and seemed to lose itself in the bicipital groove. Although the dissection was reasonably easy, for the most part, the capsule was perforated at two or three points. A yellowish mass comparable to well cooked, mashed sweet potatoes, escaped through these rents. The mass

was finally excised, sharp scissors being required to detach it from its lower and upper attachments. After the mass had been removed, the same kind of yellowish material escaped from the bicipital groove. It was evident that this mass and its contents were situated in the sheath of the tendon of the long head of the biceps muscle. The tendon itself did not look normal. Instead of being white and glistening, it was red in spots, instead of running straight upward, it bulged at one point. This bulge was made up by an almond-shaped mass, which was removed for diagnosis. It represented a node in the tendon and was movable. A few strips of the tendon and its sheath, which were red and frayed, were also removed for diagnosis.

An olecranon bursa the size of a large walnut was present over the right elbow. It had a thick capsule. The contents of the bursa were exactly like those found in the tendon sheath of the biceps muscle.

Both wounds healed by primary intention, and the patient left the hospital within four days. There was no subsequent evidence of lack of repair of the tissues.



Fig 4—Low power magnification of a section showing an area of necrosis and granulation tissue surrounded by giant cells.

Pathologic Report—The first intimation about the true nature of the tumor mass came from Dr. I. Davidsohn, the hospital pathologist, who recognized in the histologic picture a syphilitic pattern.

The tumor was sausage shaped (6 by 2 cm). It consisted of a thin capsule (1 mm) with a red, smooth, glistening outer surface, with deposits of a soft yellow material on the inner surface. About 2 cm above the proximal end of the tumor, an almond-shaped mass was found attached to the inner surface of the sheath of the long head of the biceps muscle. It measured 24 by 19 by 4 mm. It was pink, with yellow areas and strands of loose connective tissue attached to it. The sectioned surface was gray. Several pieces of membranous red tissue measured about 8 by 5 by 2 mm.

Microscopic Report—A thick layer of granulation tissue was found. Large masses of lymphocytes mixed richly with plasma cells were present in accumulations as well as diffusely. The largest accumulations were at the periphery of the capsule just below the fat tissue. The relation of these massive accumulations to blood vessels was intimate and striking, not unlike the picture seen in the adventitia of the aorta in cases of syphilitic aortitis. There was lymphocytic and leukocytic infiltration in the wall. Amorphous material in the innermost layer of the wall showed the type of necrosis seen in the contents of gummatous lesions. Sections from the node attached to the sheath of the tendon of the biceps muscle showed in some places, at the periphery, similar thick collagenous fibers infiltrated with lymphocytes and plasma cells.

Frozen sections from the amorphous contents of the bursa revealed droplets of sudanophilic material.

The changes were compatible with a syphilitic granuloma.



Fig 5—Higher magnification of the section presented in figure 4, showing many giant cells at the border of the necrotic area.

Olecranon Bursa Pathologic Report—The specimen labeled bursa of the olecranon was a sac, irregularly shaped, measuring 55 by 50 by 8 mm, with club-shaped projections extending into the bursal cavity. When the cavity was opened it was seen to be filled with a yellowish, soft, amorphous tissue, similar to the material which was present in the specimen from the arm. A surface sectioned through the club-shaped projections showed similar contents in the center of the cavity, with a translucent white tissue in the walls surrounding it.

Microscopic Report—Sections showed areas of necrosis surrounded by granulation tissue in the midst of thick layers of dense fibrous tissue. The necrotic material in the center of the nodes was eosinophilic, it was amorphous and caseous with an admixture of

some of the cells from the granulation tissue, which formed a wall around it. Among the fibroblasts, there were present relatively large numbers of giant cells with peripherally located nuclei, which were oval and vesicular, with their long axes arranged parallel and radially. The giant cells resembled those seen in tuberculosis and in gummas. The picture was characteristically that of a syphilitic gumma.

SYPHILITIC BURSITIS

This entity was first mentioned by Verneuil,⁹ in 1866 and 1877. In 1876, the elder Keyes²⁰ collected 14 cases from the general literature and analyzed 27 cases. He published an article—"Syphilis as Affecting Bursae." Keyes, Jr., reported 5 cases, 2 of which were included in the elder Keyes' article. The classic article of Churchman²¹ awakened interest in this condition, and he coined the term "luetetic bursopathy of Verneuil", in recognition of Verneuil's early description and the emphasis placed on syphilis of bursas. Codman stated "I have never recog-



Fig 6—Two spirochetes are shown in an area of necrosis.

nized a case of syphilitic bursitis in the shoulder but I have seen 2 cases of syphilitic ulcer, which presumably involved the subcutaneous bursae."

The British literature is totally silent on syphilitic bursitis. This silence is strange, since syphilitic diseases of joints have been well studied by the British. Symmetric synovitis of the knee in congenital syphilis has been known in England as Clutton's disease. Syphilitic involvement of joints was mentioned in England as early as 1498 by Peter Martyr, but was actually described by Ricket in 1853.

The interval between the primary lesion and the development of syphilitic bursitis varies from a few months to ten years. According to Churchman's tabulation, in 9 cases syphilitic bursitis

²⁰ Keyes, E. L., Sr. *Am J M Sc* 71:340, 1876.

²¹ Churchman, I. W. *Am J M Sc* 138:371, 1909.

occurred in the secondary stage of syphilis and in 17 in the tertiary stage

Patients with syphilitic bursitis have either no pain or only very slight pain. Indolent bursitis without a history of trauma should be suspected as being due to syphilis. Occasionally housemaid's knee has proved to be syphilitic. Indolent bursitis about the knee or the elbow in children with Hutchinson's triad should be suspected as being syphilitic. Roentgenograms are of no value, since the process does not involve the adjacent bone.

In the differential diagnosis between syphilitic bursitis and other entities, tuberculosis has been considered. However, according to Barnard,²² tuberculosis attacks persons in the extreme age groups, whereas syphilis attacks, as a rule, middle-aged persons.

The bursas most commonly involved are the prepatellar, the subpatellar and those about the elbow.

Pathologically, a syphilitic bursa shows hyperplasia of connective tissue with subsequent degeneration of its contents: yellowish, viscid, coagulable fluid (Garner and Schoch²³). If syphilitic bursas break down, deep ulcers or projecting fungating granulation masses form.

²² Barnard, H. L. *Clin J* **23** 188, 1904.

²³ Garner, V. C., and Schoch, A. G. Syphilitic ursoopathy of Verneuil, *Arch Dermat & Syph* **24** 591 (Oct) 1931.

Treatment consists in most cases in surgical removal, as the surgeon rarely suspects the real nature of the disease. The older syphilologists obtained many cures by using merely mercury and iodides. According to Churchman, this type of mixed treatment brought satisfactory results in about forty-six days.

CONCLUSIONS

Syphilis of tendons and bursas should be suspected more often in the diagnosis of tendinitis and bursitis.

The reasons for the scarcity of reports in modern literature as contrasted with the older literature are (a) the adequate and more universal treatment of syphilis with arsenicals and bismuth, which either modify or obviate the pathologic changes of syphilis, and (b) the intense diagnostic acumen of the older syphilologists in the absence of serologic tests.

In the case of syphilis of the tendon of the long head of the biceps muscle and of the olecranon bursa herewith presented, for the first time, the diagnosis of syphilis of these structures has been, I believe, definitely proved by the presence of *Treponema pallida* in the granulation tissue.

The tendon of the long head of the biceps muscle is more vulnerable than other tendons to both specific and nonspecific infections.

TUBERCULOUS ABSCESS OF THE THYROID GLAND

REPORT OF A CASE AND REVIEW OF THE LITERATURE

CAPTAIN R W POSTLETHWAIT AND CAPTAIN PHILIP BERG JR
MEDICAL CORPS, ARMY OF THE UNITED STATES

Formation of an abscess in the thyroid gland is an infrequent manifestation of tuberculosis. Rankin and Graham stated that "such progression of the disease (into cold abscess) is extremely rare." In a review of the literature we have been able to find only 26 cases. No reported case is similar to the one detailed in our paper in that a tuberculous abscess of the thyroid developed in this patient during the secondary stage of syphilis.

Coller and Huggins stated that two types of tuberculosis of the thyroid gland are seen: miliary and caseating. The miliary type is found with generalized tuberculous infection. In the caseating type the gland may necrose and soften to form masses of tuberculous caseating material or may liquefy to form a cold abscess. Lindsay and Mead reviewed the literature in 1934 and found recorded about 255 cases of tuberculosis of the thyroid. Of these tuberculous conditions, 25 were discovered at operation or on histologic study of the gland following operation. The remaining 130 were found at autopsy and consisted chiefly of miliary tubercles of the thyroid associated with acute generalized miliary tuberculosis. In 1933, Van Ravenswaay and Van Ravenswaay collected 107 cases in which tuberculosis of the thyroid was discovered at operation. During our search for reports of tuberculous abscess of the thyroid, we found 21 additional cases of tuberculosis of the thyroid reported since 1933, in 4 of which abscesses occurred (Tinker, Dean and Hall, Dinsmore, Ruthe, Louria and Louria, Keynes, Uraz, McGregor and Peacock, Phillips and Waldron, Baz and Perrin, Hare and Simpson, Comando). These do not include reports of the miliary type, which appears to be of less clinical interest.

To the two types discussed by Coller and Huggins might be added the sclerosing form, as reported by Budd and Williams, by Higgins and by others. In this type the thyroid glands are small, fixed and hard and are thought to represent arrested or healed tuberculosis. Budd and Williams, however, stated that "sclerosing tuberculosis of the thyroid results from circulating toxins." Jaffe reported 4 cases in which the histologic changes "are identical with those

described as a benign, sclerosing form of tuberculosis of the thyroid." He stated the belief that these conditions are the result of focal revolutionary changes and are nontuberculous. Therefore, some doubt now exists as to the actual cause of the sclerosing type.

Excellent reviews of tuberculosis of the thyroid were published by Coller and Huggins in 1926, Rankin and Graham in 1932, Van Ravenswaay and Van Ravenswaay in 1933 and Lindsay and Mead in 1934. However, no paper has been devoted to tuberculous abscess alone, and no review has contained all the recorded cases of tuberculous abscess of the thyroid. For this reason, the reported cases are abstracted briefly.

CASE 1 (Schwartz)—The patient was a 30 year old man who complained of swelling in the neck, dysphagia and dyspnea of several weeks' duration. Examination showed swelling of the right lobe of the thyroid, with deviation of the trachea to the left. The right pupil was smaller than the left, and there was paralysis of the right vocal cord. No tuberculosis was found elsewhere. Incision and drainage of the cold abscess of the right lobe yielded 60 to 70 cc of thick, yellow, granular pus. The patient recovered. In a guinea pig inoculated with the pus tuberculous lesions were produced.

CASE 2 (Rolleston)—The patient was a 23 year old woman who had paraplegia, associated with tuberculosis of the first lumbar vertebra and of the upper part of the sacrum. There was also pulmonary tuberculosis. During life there were no symptoms referable to the thyroid gland. At autopsy there was found an abscess of the left lobe of the thyroid with two openings into the esophagus. The lymph nodes of the neck were not involved.

CASE 3 (Fraenkel)—The patient was a 55 year old woman who had had swelling of the neck for several months. Hoarseness, dyspnea and dysphagia were present. A diagnosis of malignant tumor was made. Attempted extirpation of the thyroid was extremely difficult, and the patient died shortly afterward of persistent mediastinitis. Autopsy showed a tuberculous abscess of the right lobe of the thyroid gland and associated lymphatic tuberculosis.

cold abscess of the thyroid. He was cured after the operation but died some time later from osseous tuberculosis and septicemia.

CASE 5 (Roger and Garner)—The patient was a 34 year old woman who had pulmonary tuberculosis and tuberculous pharyngitis. She was admitted to the hospital during the last trimester of pregnancy and died seventeen days after delivery. During life there were no symptoms referable to the thyroid itself. At autopsy there was a cavity in the pyramidal lobe, which contained thick pus. Tubercle bacilli were found in this material.

CASE 6 (Clairmont)—The patient was a 2 year old boy who had previously been well. Seventeen days before his admission to the hospital the mother noted slight swelling of the thyroid, and ten days before admission the swelling increased and was accompanied by restlessness and slight fever. Examination on admission showed a swelling, the size of a walnut, in the midline in the region of the thyroid gland. This was firm, smooth and tender; it was displaceable in either direction, but more so horizontally, and it moved with swallowing. At operation an abscess containing thick gray fluid was found. The cavity was curetted and packed. Two fistulas followed which required excision, but the patient eventually recovered. Histologic examination showed tuberculosis.

CASE 7 (Pupovac)—The patient was a 42 year old man who had noted a walnut-sized, painless swelling in the middle of the neck after coughing seven months previously. Gradual enlargement occurred. Examination showed a swelling the size of a goose egg, which was soft, smooth and fluctuant. There were also signs suggesting tuberculosis in the apex of the left lung. A diagnosis of cold abscess was made, and aspiration yielded thin pus. At operation the wall of the abscess and the remainder of the isthmus were excised with radical excision of the lymph nodes of the neck. The wound healed well, and histologic examination showed tuberculous granulation and tubercles in the wall of the abscess.

CASE 8 (Corner)—The patient was a 9 year old girl who had had swelling of the neck for one year. Examination showed the right lobe of the thyroid to be enlarged. The lower pole was soft and fluctuant. There was a sinus at the apex of the left lobe. At operation an abscess of the right lobe was opened and "one to two drachms of pus" evacuated. Sections of the wall of the abscess showed chronically inflamed thyroid tissue and tubercles. No tuberculosis was found in the lungs prior to operation. The patient died seven months later from tuberculous meningitis and acute generalized tuberculosis, the wound having failed to heal.

CASE 9 (Lediard)—The patient was a 21 year old man. The signs and symptoms were not stated. No tuberculosis, however, was found elsewhere in the body. At operation an ounce or more of seropurulent material was removed from the left lobe of the thyroid gland. Recovery was prompt. No tubercle bacilli were found in the pus, and cultures were negative. Histologic examination of excised tissue showed tubercles.

CASE 10 (von Schiller)—The patient was a 17 year old youth who had chronic pulmonary tuberculosis. He first noted a tumor the size of a nut in the left lobe of the thyroid. This gradually increased over a period of several months to the size of a fist. Dyspnea was present. The enlargement was soft. At operation a cold abscess, containing 90 cc of pus, was evacuated. Tubercle bacilli were found in the pus. The patient recovered.

CASE 11 (Lenormant)—The patient was a 40 year old man who had a cold abscess of the isthmus of the thyroid, the size of a black walnut. He also had a cold abscess over the right greater trochanter. Incision and drainage of the abscess of the thyroid were carried out. A fistula formed which persisted for about two and one-half months. No laboratory confirmation of the cause of the abscess was given.

CASE 12 (Halstead)—The patient was a 28 year old woman who had had a swelling in the neck for one year. It gradually enlarged to the size of a small orange, and a month before operation it caused pain, dyspnea and dysphagia. Poultices were applied, and after a few days an opening formed, discharging thick pus. This was followed by discharge of large quantities of pus and caseating material at intervals of a few days, without a decrease in the size of the mass. At operation an abscess cavity of the left lobe of the thyroid gland was found, extending down behind the sternum. Prolonged drainage occurred but was followed by recovery. No organisms were found, but histologically tuberculosis was present.

CASE 13 (Pollag)—The patient was a woman of 59 years. There was a family history of tuberculosis, and her past history suggested pulmonary tuberculosis. She had had a goiter from childhood. Three years before she began having difficulty with the right knee. She was admitted to the hospital, and femoral amputation was carried out for tuberculosis of the right knee joint. Examination at this time showed an infection in the apex of the left lung. There was a moderate enlargement of the thyroid, with a walnut-sized node in each lobe. Nineteen days after amputation of the leg the skin over the thyroid gland became red, warm and tender. Seven days later fluctuation appeared. At operation thin fluid pus was obtained and an abscess of the isthmus drained. The patient eventually recovered. Tubercle bacilli were present in the pus, and the wall of the abscess contained tubercles histologically.

CASE 14 (Pollag)—The patient was a 74 year old woman whose neck had always been large. Five days before admission there was increased swelling and then a rapid increase in size, after which she came to the clinic. A diagnosis of "cystic struma with intracystic blood" was made. Examination showed the right lobe to be moderately enlarged and firm. In an area nearer the midline on the right there was another soft fluctuant swelling. The skin was red in the center, bluish red in the surrounding area and entirely blue around the periphery. No tenderness was present. Aspiration was followed by incision and drainage, from which a creamy exudate from gray-green to brownish in color was

obtained. The patient recovered. The aspirated pus contained tubercle bacilli.

CASE 15 (Labey)—The patient was a 76 year old woman who had a large goiter with symptoms of suffocation. The left lobe of the thyroid was involved, extending behind the sternum and pushing the trachea and the larynx to the right. Fluctuation was present. Incision was made, and caseous pus was found filling a cavity in the left lobe. The cavity extended into the upper mediastinum. The left lobe and the isthmus were removed, the mediastinal tract curetted and several hard masses in the right lobe removed. Histologic examination showed tuberculosis.

CASE 16 (Jean)—The patient was a 42 year old man who complained of swelling in the neck, with hoarseness and dysphagia of several months' duration. A little to the right of the midline there was a round tumor, which felt cystic and was tender. At operation pus was obtained, the right lobe removed and the wound closed without drainage. This remained healed for seven months. Tubercle bacilli were found in the pus. The abscess was thought to be secondary to pulmonary tuberculosis.

CASE 17 (Vallata)—The patient was a 62 year old woman who had had a goiter for sixteen years. Several weeks prior to her admission to the hospital pain developed. This was relieved by hot packs but later returned and was accompanied by dysphagia and dyspnea. Occipital headache was also present. When she entered the hospital her general condition was poor. There was slight fever. The thyroid was diffusely enlarged, the left lobe more so than the right. The left lobe was firm and tender. Hot packs were applied for seven days, after which distinct fluctuation appeared. Incision and drainage were done, and an odorless seropurulent liquid was obtained. The patient recovered. No organisms were found. Histologic examination showed tuberculosis.

CASE 18 (Jones)—The patient was a 64 year old man with a history of rapid increase of swelling in the neck over a period of three months. Dysphagia and hoarseness were present. Examination showed a tumor over the isthmus. This moved on deglutition and was tense, encapsulated, nonfluctuant and not painful, the skin was not adherent. The whole tumor was freely movable up and down but not laterally. At operation the capsule was broken during dissection, and there escaped a thick, creamy, yellow pus, containing small caseous particles. The wound healed with ultraviolet therapy. No tubercle bacilli were found, but a guinea pig inoculated with the pus died of generalized tuberculosis.

CASE 19 (Dimitza)—The patient was a 69 year old woman who had had a goiter for thirty years. Striking growth, with pressure on the surrounding structures, had occurred in the two to three months prior to admission. Loss of weight had occurred. The swelling was principally on the left side. Aspiration produced a purulent, grayish brown liquid. Under intensive roentgen therapy a large opening formed at the site of a puncture made with a needle. This gradually healed over a period of eighteen months. Tubercle bacilli

were obtained on culture of the pus, and tuberculosis developed in a guinea pig inoculated with the pus.

CASE 20 (Starlinger)—The patient was a 2 year old boy. For fourteen days there had been swelling of the neck, with some respiratory difficulty. Examination showed a walnut-sized mass on the right side. This was smooth and not tender and moved with swallowing. Slight stridor was present. At operation greenish yellow fluid was found. The cavity was packed. A fistula formed and was later excised, and healing finally occurred. One year later the patient was seen and appeared slightly myxedematous. Cultures of the pus were negative, but histologic examination of the tissue showed tuberculosis.

CASE 21 (Starlinger)—The patient was a 64 year old man who had had severe dyspnea and increase in the size of the neck for one year. For six months there had been rapid growth of the goiter, dysphagia and pain radiating to the back of the head. He also noted decreased hearing. Examination showed a tumor the size of a fist on the left side. This was firm, smooth, tender and elevated on swallowing. There was paralysis of the left recurrent nerve, and the trachea deviated to the right. At operation excision of the tumor, which extended behind the esophagus, was attempted, but the abscess was opened and an esophageal fistula was found. Therefore, extirpation of the left lobe of the thyroid was carried out, and gastrostomy had to be done. The patient died four months later of erosion of a large vessel. At autopsy there were found old tuberculous peritonitis, pulmonary tuberculosis and tuberculosis of the thyroid gland.

CASE 22 (Starlinger)—The patient was a 48 year old man who had had a goiter for thirty years. Three weeks before admission to the hospital he had noted pain in the neck, especially with cough. After fifteen days the swelling became firm. The patient lost about 22 pounds (10 Kg) during the acute phase of the illness. Examination showed on the right side of the neck a tumor the size of a fist, which was firm and irregular and moved with swallowing. The lower pole was tender. At operation the abscess was accidentally opened, and copious pus appeared. The right lobe of the thyroid was removed, and the resulting wound was packed and eventually healed. Recovery occurred. Histologic examination showed tuberculosis.



Fig 2—Photomicrograph of the tuberculous granuloma in tissue removed at the second operation (United States Army Medical Museum specimen 77603)

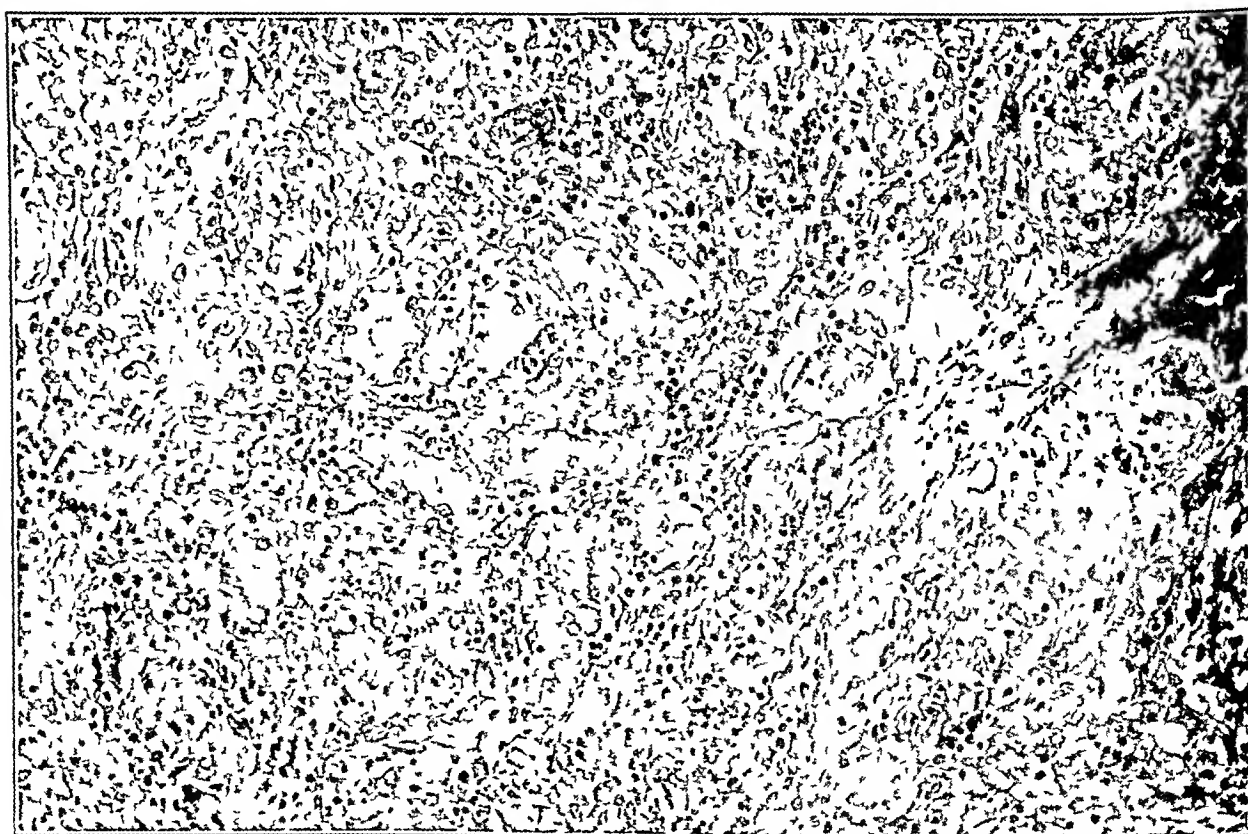


Fig 3—Photomicrograph of remnants of thyroid follicles in tissue removed at the second operation (United States Army Medical Museum specimen 77602)

three weeks' duration. The soreness had not been severe at any time, but dysphagia had been persistent. During this time he had also noted enlarged nodes in the back of the neck and the gradual appearance of a mass in the region of the thyroid gland. Five days before his admission an ulcer had developed on the penis. His last sexual intercourse had been with a prostitute one month previously. The past history was irrelevant. There had been no previous enlargement of the thyroid.

On examination the patient did not appear acutely ill. There was no fever or tachycardia. The tonsils were enlarged, injected and superficially ulcerated. A firm, smooth, slightly tender mass, about the size of a small lemon, was present in the region of the right lobe of the thyroid. This moved with swallowing and was not attached to the skin. The lymph nodes in the anterior cervical region were enlarged but not tender. In the right para-frenal area of the penis a small, superficial, sharply circumscribed, painless ulcer was seen.

Accessory clinical data showed a red blood cell count of 4,400,000, a hemoglobin content of 90 per cent and a white cell count of 6,700, with 75 per cent polymorphonuclear forms. Urinalysis gave normal results. Material from the penile ulcer showed *Treponema pallidum* on dark field examination. Kahn reactions were repeatedly positive. A Frei test gave a negative reaction and a roentgenogram of the chest showed nothing abnormal.

The day following the patient's admission, macular lesions were noted over the antecubital regions, the back and the legs. Antisyphilitic therapy was given, the patient receiving an arsenical (mapharsen) intravenously twice weekly and bismuth subsalicylate intramuscularly once a week. With this treatment the tonsillitis rapidly subsided, the ulcer on the penis healed and the enlarged lymph nodes became smaller. The right lobe of the thyroid, however, became a little larger and remained firm and only slightly tender. The skin overlying the right lobe was somewhat reddened. No fixation of the mass was present. There were little pain, no dysphagia and no limitation of extension of the neck. No systemic changes were present except an elevation of temperature from 99.0 to 99.8 F in the afternoons. The basal metabolic rate was +4. Approximately three weeks after the patient entered the hospital fluctuation in the mass was elicited.

Aspiration of the right lobe of the thyroid yielded purulent material. The abscess was then incised under local anesthesia, and about 75 cc of thick, yellowish gray purulent material was obtained. The abscess cavity outlined accurately the entire right lobe of the thyroid. An attempt was made to encourage healing by granulation from the bottom of the wound by packing the abscess cavity with petrolatum gauze. Despite this a sinus formed and was excised ten weeks after the original incision. Another sinus formed, and final healing did not take place until four weeks later. The wound has remained healed since the patient's discharge from the hospital, four months prior to the time of writing. He feels well and is able to carry on his

full duties as a soldier. There is nothing to suggest myxedema and no evidence of tuberculosis elsewhere in the body.

Unfortunately the material obtained at operation was not stained for acid-fast bacilli nor inoculated into a guinea pig. Dark field examination revealed no spirochetes. Routine cultures of the pus were sterile. Later cultures of the discharge during healing all showed *Staphylococcus aureus*. A small mass of necrotic material removed at the first operation showed no cellular detail on histologic study, so that no diagnosis could be made. When the sinus tract was removed the excised tissue showed tubercles and a few structures suggesting thyroid follicles. Special stains of this tissue showed acid-fast bacilli.

COMMENT

Louria and Louria stated "For undoubted proof of the existence of tuberculosis of the thyroid gland, one would expect characteristic histological evidence, substantiated by the demonstration of tubercle bacilli on culture of the tissue or through guinea-pig inoculation." However, Hedinger, Lediard, Corner, Halstead, Mosiman, Plummer and Broders and most subsequent investigators have accepted the histologic evidence as adequate for a diagnosis of tuberculosis.

In the case presented some doubt may be justifiably expressed of the diagnosis of tuberculosis in the presence of secondary syphilis. Van Ravenswaay and Van Ravenswaay stated "It is probable that in lesions of clinical importance, after lues has been excluded, a diagnosis of tuberculosis can be made from the microscopic picture with a high degree of accuracy." On a histologic basis alone, therefore, we would be unable to differentiate absolutely between syphilis and tuberculosis. Tubercle bacilli, however, were demonstrated in the excised tissue, and on this basis there would seem to remain little doubt as to the cause of the lesion. It may be mentioned that we were unable to find a reported case in which acute suppurative thyroiditis developed during primary or secondary syphilis.

It is possible, however, that during the acute phase of syphilis a locus minoris resistentiae was created in the thyroid by the syphilis, thereby lowering resistance to such a point that the tubercle bacilli were able to initiate a pathologic process. Our inability to demonstrate tuberculosis elsewhere in the body does not detract from the exactness of the diagnosis. Rankin and Graham found no tuberculosis elsewhere in their 21 cases, and no mention of tuberculosis elsewhere in reports of 91 of 97 cases in which adequate information was available. In only 9 of the 26 reported cases of tuberculous abscess of the thyroid were tuberculous lesions found elsewhere in the body.

ROLE OF ALLERGY IN DELAYED HEALING AND IN DISRUPTION OF WOUNDS

I ANTIGENICITY OF CATGUT

HOWARD C HOPPS, M D

CHICAGO

The general incidence of disruption of wounds has been estimated to be from 1.5 to 2 per cent following abdominal operations.¹ Over 1,400 cases of such disruption have been recorded.² Since approximately 35 per cent of patients suffering such disruption of wounds die,³ it can be seen that this complication presents a major surgical problem and accounts for a considerable number of postoperative deaths. The increased morbidity which attends breakdown or delayed healing of wounds is obvious. Not only is the time of hospitalization and of recovery greatly prolonged, but the incidence of postoperative hernia is greatly increased.

In order to understand the mechanism of dehiscence of wounds it is necessary to understand the processes which normally occur to bring about the healing of surgical wounds. The reader is referred to the excellent review article of Arey⁴ and to the papers of Carrel,⁵ Harvey,⁶

Loeb⁷ and others⁸ for a discussion of these fundamental processes.

Of the predisposing or causative factors which lead to breakdown of wounds, it may be said that age and sex are probably not significant, since these vary widely, depending on the series of cases studied.⁹ Similarly, the site of abdominal incision does not appear to be an important factor. Much has been written about the technic of closure of wounds with respect to decreasing the incidence of disruption, and some surgeons have reported that as the result of using certain prescribed technics the incidence of breakdown of wounds in their patients is almost nil.¹⁰ Yet these same technics fail in the hands of other, equally skilled, operators. Suture material too has come under scrutiny as a possible factor leading to evulsion of wounds.¹¹ It is common

From the Department of Pathology, University of Chicago

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opinion that wounds repaired with catgut are more liable to disruption than are wounds repaired with nonabsorbable material, such as silk, silkworm gut or wire, and yet many cases of breakdown of wounds have been reported despite the use of these nonabsorbable materials¹² In a series of 22 cases reviewed by Glenn and Moore^{3c} the incidence of disruption of wounds following closure with catgut was 0.68 per cent, as compared with 0.61 per cent following the use of silk

As fairly well established causes of disruption or delayed healing of wounds, the following may be listed¹³

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1 Faulty surgical technic or other factors leading to a reduced supply of blood to the healing wound

2 Inadequate closure of the wound, particularly if this allows for an opening in the peritoneal membrane through which a wedge of omentum may be introduced

3 Abdominal distention, coughing, violent activity on the part of the patient, etc, in the early postoperative period, leading to actual pulling apart of the margins of the wound

4 Infection of the wound

5 Hypoproteinemia

6 Hypovitaminosis C

7 Such constitutional states as inanition, cachexia, severe anemia and jaundice

In an appreciable number of instances, however, none of these factors appears to be operating and yet the wound breaks down or heals poorly It is for this group that allergy to catgut has been suggested as an important, if not the most important, causative factor Babcock¹⁴ was one of the first surgeons in this country to consider allergy to catgut seriously as an important causative factor in delayed or abnormal healing of surgical wounds He stated that allergic reactions to catgut may be due to its major protein constituent (derived from sheep), to unremoved bacterial products or to special toxic substances In order to avoid an allergic reaction and its untoward effects, he advised the use of silk suture material in all clean wounds Hinton^{1b} demonstrated positive reactions to catgut extract in 9 of 12 patients who had been previously operated on and concluded, "it seems logical to assume that a certain percentage of patients might be considered allergic to catgut" Whipple and Elliott¹⁵ from their studies expressed "little doubt but that the local reaction in patients allergic to catgut predisposes to infection and favors wound disruption" Langston¹⁶ followed 54 patients during the various stages of thoracoplasty and stated that the appearance of the wound was found to reflect directly the severity of the pre-

Obst **69** 745, 1939 Wolfer, J A Surgical Aspects of Vitamin C Deficiency, *S Clin North America* **20** 225, 1940 Hartzell and Winfield^{1a} Hinton^{1b} Melenev and Howes^{1c} Jenkins² Maes, Boyce and McFetridge^{2b} Colp^{3a} Grace^{3c}

14 Babcock, W W Catgut Allergy, with a Note on the Use of Alloy Steel Wire for Sutures and Ligatures, *Am J Surg* **27** 67, 1935

15 Whipple, A O, and Elliott, R E The Repair of Abdominal Incisions, *Ann Surg* **108** 741 1938

16 Langston, H T The Problem of Catgut Sensitivity and Its Relation to Wound Healing *Ann Surg* **115** 141, 1942

operative reaction to the cutaneous test Bellas¹⁷ reported allergic cutaneous reactions to catgut in some of his patients and was sufficiently impressed by reactions to catgut sutures to say that "incisions heal not because of, but in spite of catgut" From a study of 50 patients in whom disruption of surgical wounds developed Fallis^{3d} concluded that "the clinical picture in the non-infective cases suggests an allergic reaction"

Many experimental studies have been made to determine whether or not allergy to catgut is an important cause of disruption of wounds They have been positive and equally controversial in their results and in the conclusions to which they lead Marchesani¹⁸ obtained allergic inflammatory reactions to catgut implanted beneath the skin or to catgut extract placed in the conjunctival sac in animals sensitized to catgut and succeeded in demonstrating an antigenic relationship between catgut and sheep serum by anaphylactic studies In the following year, 1933, Moriconi¹⁹ was unable to confirm these results He failed to demonstrate allergic inflammation or humoral antibodies in rabbits into which had been injected either plain or iodized catgut Gratia and Gilson²⁰ sensitized guinea pigs to sheep serum, to horse serum and to a mixture of these two antigens After the introduction of strands of catgut or a powdered suspension of catgut intraperitoneally, they stated that the reaction "appears a little less intense in the guinea pigs sensitized to the serum of horse than in those sensitized to the serum of sheep" These reactions were much more intense than those exhibited by normal guinea pigs Catgut which was soaked in antisheep rabbit serum for a long time provoked but a slight (normal) reaction when implanted into animals sensitized to sheep serum The authors concluded that catgut is an antigen which will cause an Arthus reaction when introduced into an animal sensitized to sheep serum and stressed what they considered the important relationship of such a reaction to the formation of postoperative adhesions Frugoni,²¹ however, was unable to demonstrate humoral antibodies in rabbits supposedly

allergic to catgut, nor could he demonstrate anaphylactins in guinea pigs which had been treated with catgut After the reintroduction of catgut into the peritoneal cavities of sensitized animals, the only reactions which developed appeared to be nonspecific—responses to foreign material Kraussl, Kesten and Cimiotti²² injected into guinea pigs plain catgut, chromicized catgut and chromic acid Subsequently abdominal incisions were made and repaired with catgut From 25 to 35 per cent of each of the three groups of sensitized animals had wound disruption, as against none in the control group Tests to detect cutaneous sensitivity were made on 30 patients who had experienced disruption of wounds, and 19 of these patients gave positive reactions to one or more of the test extracts More recently, Pickrell²³ was unable to induce a state of hypersensitivity to catgut in rabbits or guinea pigs by repeated injections of ground catgut or by implantation of strands of catgut He stated "One can finally conclude that although catgut, like any other suture material acts as a foreign body and causes slight leukocytic response, it does not act as an antigen to induce the hypersensitive state" In contrast to this Vaccaro and Cabezas²⁴ reported that catgut does possess antigenic and sensitizing properties and that aseptic inflammation, production of fibrous nodules and adhesions result from the intraperitoneal implantation of catgut in sensitized animals They found that in such animals absorption of catgut was delayed

The experiments to be described here were designed to determine whether or not a state of hypersensitivity to catgut can be induced and, if so, what effect such hypersensitivity has on the healing of surgical wounds repaired with catgut sutures

MATERIAL AND METHOD

As a working hypothesis it was considered likely that catgut per se, because of the probable denaturation of protein and the chemical alteration sustained during preparation and because of its relative insolubility, is a poor antigen It was postulated that sheep serum or sheep intestine might be more effective in stimulating the formation of antibodies to catgut than catgut itself For these reasons the following materials were used as antigens

17 Bellas, J E The Influence of Sutures upon Operative Wounds Review of Cases, *Ann Surg* **112**, 1940

18 Marchesani, O Ueber Catgutnaphylaxie, *Ber u d Versamml d deutsch ophth Gesellsch* **49** 233, 1932

19 Moriconi, L Ricerca di proprieta antigena del catgut *Rassegna internaz di clin terap* **14** 2, 1933

20 Gratia, A, and Gilson, O Le phenomene d'Arthus, au catgut, cause insoupconnee d'accidents post-operatoires, *Mém Acad roy de med de Belgique* (no 2) **25** 1, 1934

21 Frugoni, P Sulla supposta allergia da catgut, *Arch ital di chir* **43** 334, 1936

22 Kraussl, C J, Kesten, B M, and Cimiotti, J G The Relation of Catgut Sensitivity to Wound Healing, *Surg, Gynec & Obst* **66** 628, 1938

23 Pickrell, K L Studies on Hypersensitivity to Catgut as a Factor in Wound Disruption, *Bull Johns Hopkins Hosp* **64** 195, 1939 Pickrell, K L, and Clay, R C Wound Disruption and Catgut Allergy. An Experimental and Clinical Study, *Surgery* **15** 333, (Feb) 1944

24 Vaccaro, H, and Cabezas V, J Alergia al catgut y produccion de adherencias Estudio experimental y clinico, *Rev med de Chile* **70** 750, 1942

1 Plain surgical catgut (a heterogeneous mixture of remnants collected from the operating room) treated with several changes of acetone and with petroleum benzene (petroleum ether), dried under reduced pressure and ground to a fine powder

2 Sheep intestine, obtained fresh from the stock yards, thoroughly washed, freed of mucosa and fat, minced, treated with acetone and ether, dried and ground to a fine powder

3 Sheep serum

Several extracts of catgut were prepared, the most potent of these was obtained by mixing finely powdered catgut with a tenth-molar solution of sodium hydroxide (10 cc per gram of catgut), stirring constantly for five minutes, quickly centrifuging and then adding tenth-molar hydrochloric acid to bring the supernatant fluid to a pH of 7.2 to 7.5. The solution was concentrated by evaporation from a cellophane bag. The final yield was 7 cc of extract for each gram of powdered catgut. Although this solution was clear, it gave strongly positive biuret, xanthoproteic and Millon reactions for protein and yielded a heavy precipitate on the addition of tungstic acid.

Thirty-two rabbits and 36 guinea pigs were used in the first part of this study. Rabbits were given multiple subcutaneous and intraperitoneal injections of sheep serum, sheep intestine or catgut, a single dose consisting of 1 to 2 cc of sheep serum or 80 to 100 mg of the dried powder made into a heavy suspension with saline solution. Injections were made at intervals of from five days to three weeks. Precipitin titers against sheep serum were determined by the antibody dilution method of Cannon and Marshall,²⁵ but for those against catgut and sheep intestine solid particles of these antigens were used instead of the usual coated carbon or colloidal particles.

EXPERIMENTAL STUDIES

Of three groups of rabbits, each animal received a total of seventeen injections of sheep serum, sheep intestine or catgut over a period of approximately six months, at the end of which time cutaneous tests were performed and antibody titers determined. Cutaneous tests were done after careful preparation of the test sites on the preceding day. Reactions were evaluated at twenty-four hours. In figure 1 the average reaction of each group of rabbits to (a) a tiny loop of no. 1 plain catgut implanted subdermally and (b) 0.05 cc of sheep serum injected intradermally is shown. The degree of shading represents the approximate intensity of erythema. The relative size of the lesions was determined by actual measurement. In the same groups of animals (including 6 normal controls) 1 mm of sterile plain no. 000 catgut,²⁶ thoroughly washed free of tubing fluid, was inserted into the anterior chamber of the eye. This was accomplished with the animal under pentobarbital sodium anesthesia. A specially prepared 18 gage hypodermic needle and a stylet were used. The point of the

needle was introduced into the anterior chamber, just central to the limbus, at 12 30 o'clock, with a minimum of trauma, and the piece of catgut was expelled from the lumen of the needle. Reactions were evaluated at thirty-six hours. Those animals in which traumatic inflammation was severe or in which hemorrhage occurred were discarded from the series. The reactions tended to parallel, roughly, cutaneous reactions to catgut, however, reactions to operative trauma made exact evaluation of allergic inflammation impossible. At three and one-half and seven days the lesions were again carefully examined, but in most instances nonspecific foreign body reactions tended to mask any allergic inflammation that might have been present at this time.









ANIMAL	TEST SUBSTANCE	
	CATGUT SUTURE	SHEEP SERUM
Group I Control (4)		
Group II Sheep Serum (4)		
Group III Sheep Intestine (4)		
Group IV Catgut (4)		

Fig 1—Cutaneous reactions (Arthus) to catgut and to sheep serum in normal and in sensitized animals

Humoral antibody titers against catgut and sheep serum in the various groups are shown in the table. These titers correlate well with the cutaneous reactions previously described. It is apparent that in animals treated only with catgut humoral antibodies for and cutaneous sensitivity to sheep serum develop. A comparison of the relative antibody titers of animals sensitized to sheep serum and of animals sensitized to catgut is shown in figure 2.

From these results one might assume that sheep serum, sheep intestine and catgut are equally effective in stimulating the production of antibodies to catgut, however, in a preliminary experiment, with rabbits, after seven injections of catgut or sheep intestine (compared with seventeen in the present series) a low titer precipitin against catgut was obtained of the animals treated with sheep

²⁵ Cannon, P. R., and Marshall, C. E. An Improved Serologic Method for the Determination of the Precipitative Titres of Antisera, *J Immunol* 38:365, 1940

²⁶ Johnson & Johnson, "Ethicon"

but not in the animals treated with catgut (2). Continued antigenic stimulation in the latter group did lead to the formation of demonstrable humoral antibodies to catgut.

A second series of rabbits (10) was given nine injections of a mixture of sheep serum and powdered sheep intestine subcutaneously during a period of two and one-half months. Of these animals the 2 with the highest humoral antibody titers were selected as donors of serum for passive sensitization of guinea pigs. Pooled sera of these animals agglutinated particles coated with sheep serum at a dilution of 1:1,920 (highest dilution used) and carbon particles coated with catgut extract at a dilution of 1:240. Complement-fixing antibodies for this catgut

(uterine horns) were obtained for in vitro anaphylactic studies. The horns of each sensitized animal gave a typical anaphylactic reaction to either sheep serum or catgut extract, as compared with the insignificant reactions obtained with control strips (fig 3).

From these observations it is apparent that hypersensitivity to catgut has been produced and that there is a definite antigenic relationship between sheep serum, sheep intestine and catgut

Precipitin Titers Against Catgut and Sheep Serum in Normal and in Sensitized Rabbits

<i>Precipitin Titer Against Catgut in Normal and in Sensitized Rabbits</i>		Serum Dilution							
Animal	Antigen	1 20	1 40	1 80	1 160	1 320	1 640	1 1280	
1 control	Catgut	0	0	0	0	0	0	0	
	Sheep serum	+	+	+	0	0	0	0	
2 s s	Catgut	+	+	+	+	+	+	0	
	Sheep serum	+	+	+	+	+	+	0	
3 s s	Catgut	+	+	+	0	0	0	0	
	Sheep serum	+	+	+	+	+	+	0	
4 s s	Catgut	+	+	+	0	0	0	0	
	Sheep serum	+	+	+	+	+	+	0	
5 s s	Catgut	+	+	+	+	0	0	0	
	Sheep serum	+	+	+	+	+	+	0	
6 i	Catgut	+	+	+	0	0	0	0	
	Sheep serum	+	+	+	+	+	+	0	
7 s i	Catgut	+	+	+	+	0	0	0	
	Sheep serum	+	+	+	+	+	+	0	
8 s i	Catgut	+	+	+	+	0	0	0	
	Sheep serum	+	+	+	+	+	+	0	
9 cg	Catgut	+	+	0	0	0	0	0	
	Sheep serum	+	+	+	+	0	0	0	
10 cg	Catgut	+	+	+	+	0	0	0	
	Sheep serum	+	+	+	+	0	0	0	
11 eg	Catgut	+	+	+	+	0	0	0	
	Sheep serum	+	+	+	+	0	0	0	
12 eg	Catgut	+	+	+	+	0	0	0	
	Sheep serum	+	+	+	+	0	0	0	

extract were also demonstrated. Guinea pigs (200 to 250 Gm) were given three doses of this pooled anticatgut rabbit serum intraperitoneally, (15 cc in each dose) at twelve hour intervals. Four days after the first dose of serum, each of the animals was given, via the jugular vein, 1 cc of an extract of plain catgut. Each of the 3 sensitized pigs gave a slight but definite anaphylactic reaction, characterized by ruffling of hair, dyspnea, wheezing and slight to moderate prostration. Two normal control animals gave no reaction following similar treatment. The catgut extract used in this particular experiment was weak, which fact may explain the survival of the shocked, sensitized pigs. Guinea pigs of a second group (150 to 180 Gm), virgin females, were passively sensitized as was the preceding group (they received 3 cc instead of 45 cc of anti-serum). At four days smooth muscle strips

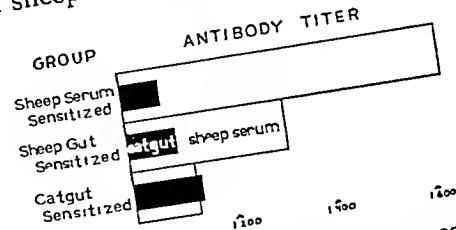


Fig 2—Antigenic relationship between catgut and sheep serum as demonstrated by antibody reactions in rabbits sensitized to sheep serum, to sheep intestine and to catgut.

The question arises, however, as to the nature of this antigenic relationship. Is sheep serum protein the only antigenic constituent of catgut, or does catgut possess, in addition, some antigenic substance not present in sheep serum? To answer this question, two groups of 6 guinea pigs (150 to 180 Gm) were given subcutaneous injections, one group receiving 0.3 cc of sheep

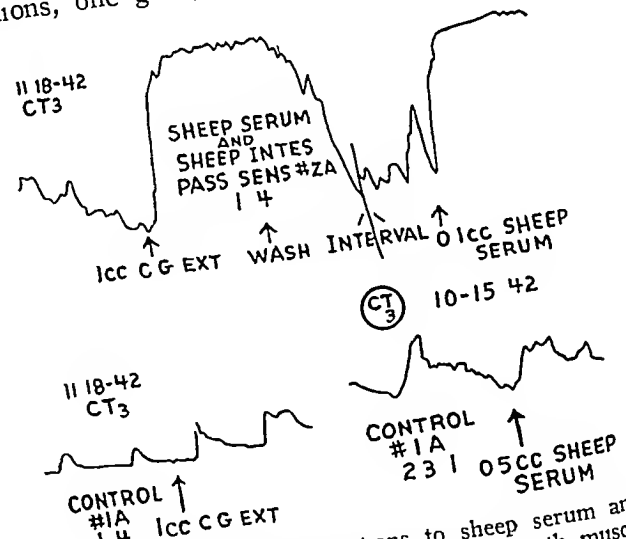


Fig 3—Anaphylactic reactions to sheep serum and to extract of catgut in preparations of smooth muscle from passively sensitized guinea pigs (sensitized to sheep serum plus sheep intestine).

serum and the other group 50 mg of powdered catgut suspended in saline solution. Three doses were given at three day intervals. Four weeks after the first injection, uterine horns were obtained for anaphylactic studies. One horn of each sensitized animal was tested with the specific substance with which the animal had been treated.

order to ascertain a state of hypersensitivity every animal gave a positive reaction. The remaining horn was treated with the other antigen, either sheep serum or catgut extract, as the case might be. In each instance an anaphylactic reaction was obtained on first exposure to this antigen. This treatment was repeated several times, with washing of the horn and an interval of recovery in between, until with the horns of the animals sensitized to catgut sheep serum no longer gave an anaphylactic reaction. In other words, antibodies specific for sheep serum in these animals sensitized to catgut had been completely exhausted. Subsequently, the strips were exposed to catgut extract, and, as illustrated

From Dr Francis O. Schmitt²⁷ highly purified preparations of sheep collagen were obtained for testing with the anticatgut rabbit serum previously described, to determine whether or not antibodies specific for collagen could be demonstrated. Some technical difficulty was encountered in preparing particles of optimum size from this substance for the determination of precipitin titers, however, one of the samples, "of very high purity," was agglutinated by anticatgut serum at a dilution of 1:80. A second sample, described as being of the "highest purity," having been treated by enzymes in the final stages of preparation, was not agglutinated by serum at a dilution of 1:10. It is possible that in this second prepa-

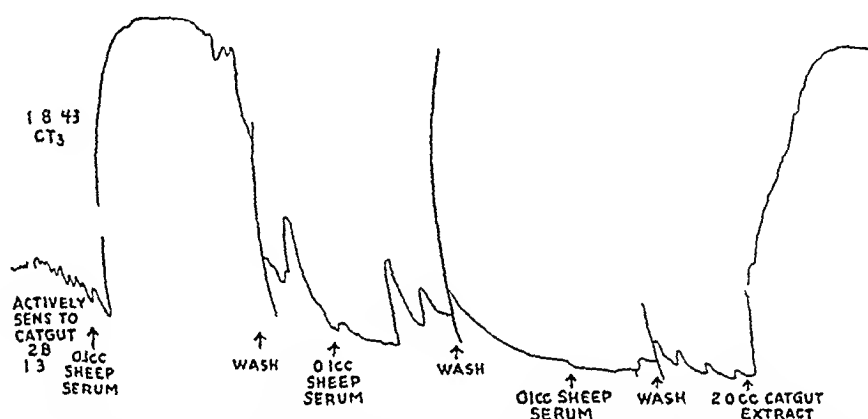


Fig 4—Anaphylactic reaction to extract of catgut in a preparation of uterine horn from a guinea pig actively sensitized to sheep serum. During the course of the three exposures to sheep serum, antibodies specific for sheep serum were exhausted.

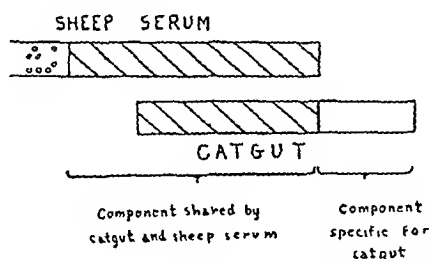


Fig 5—Probable antigenic relationship between catgut and sheep serum

figure 4, a typical anaphylactic reaction resulted. These results demonstrate that at least two groups of antibodies are elicited as a result of antigenic stimulation by catgut, one of which will react with both sheep serum and catgut and the other of which is specific for catgut. The converse of this was not established. After as many as eleven reactions to catgut extract, the uterine strip of an animal sensitized to sheep serum was still capable of slight anaphylactic response on a twelfth exposure to catgut extract, after which this strip exhibited an anaphylactic reaction (diminished) to sheep serum also. From these results it was concluded that the most likely antigenic relationship between catgut and sheep serum is that shown in figure 5.

ration of collagen enzymatic action altered antigenic constituents which may have been present. It is also possible that the positive reactions with the one sample of collagen might have been the result of some impurity (sheep serum protein).

With the demonstration that antigens from sheep serum are present in catgut, the possibility arose that perhaps antigens of sheep erythrocytes might also be present and that, since sheep erythrocytes are an excellent source of heterophile antigen, there might be some relationship between heterophile antibodies and antibodies for catgut. Such a relationship, if it existed, might be of importance, since approximately 4 per cent

²⁷ Of the Department of Biology and Biological Engineering, Massachusetts Institute of Technology.

of human beings normally possess heterophile antibodies in their blood and since during certain conditions, notably infectious mononucleosis, the heterophile antibody titer reaches a high level. It was thought that these heterophile antibodies might provide a mechanism by which persons could become hypersensitive to catgut without ever having contacted this substance or without having a manifest allergy to sheep serum. To investigate this possibility rabbits were given repeated injections of heterophile antigen (a sterile emulsion of guinea pig kidney) over a period of several months until a maximum titer of 1:480 was obtained against washed sheep erythrocytes. Cutaneous tests with catgut were made and precipitin titers against catgut determined as before. Also, portions of catgut were introduced into the anterior chambers of the eyes of these animals. In no instance was there any indication of sensitivity to catgut. Because of the rather low heterophile antibody titers of this group of rabbits, serum was obtained from persons recovering or recently recovered from infectious mononucleosis. One of these serums agglutinated washed sheep erythrocytes at a dilution of 1:1,920 (others at a dilution of 1:480). Antibodies to catgut were not demonstrable in any of these human serums.

COMMENT

From the experiments here presented, it is evident that hypersensitivity to catgut can be consistently produced experimentally in animals and that either sheep serum or catgut (or its antecedent, sheep intestine) is capable of inducing this state. Some investigators may have failed to induce sensitivity in animals following injec-

tion of catgut because too little of this substance was used and/or because the period of treatment was too short. It will be recalled that as much as 700 mg of finely powdered catgut administered over a period of one and one-half months failed to stimulate demonstrable humoral antibodies to catgut, whereas 1,700 mg of this substance given over a six month period did induce hypersensitivity (1,700 mg of catgut [dry weight] represents a 915 cm length of size no. 0 plain catgut). The effects of hypersensitivity to catgut on the healing of surgical wounds repaired with catgut sutures will be the subject for analysis in a subsequent paper.

SUMMARY AND CONCLUSIONS

Hypersensitivity to catgut has been produced in rabbits and guinea pigs, as shown by positive cutaneous reactions, positive reactions to catgut implanted in the anterior chamber of the eye and demonstration of humoral antibodies (precipitins, agglutinins, complement-fixing antibodies and anaphylactins) *in vivo* and *in vitro*.

Catgut, sheep intestine or sheep serum is capable of inducing this hypersensitive state.

In addition to antibodies which will react with either catgut or sheep serum, catgut stimulates the production of antibodies specific for itself. These antibodies specific for catgut may also be specific for collagen or for mucoprotein.

Heterophile antibodies do not react with catgut.

The effects of hypersensitivity to catgut on the healing of surgical wounds repaired with catgut sutures will be the subject for analysis in a subsequent paper.

950 East Fifty-Ninth Street

ROLE OF ALLERGY IN DELAYED HEALING AND IN DISRUPTION OF WOUNDS

II EFFECT OF SPECIFIC SENSITIVITY TO CATGUT ON REACTION OF TISSUES TO CATGUT SUTURES AND ON HEALING OF WOUNDS IN THE PRESENCE OF CATGUT SUTURES

HOWARD C HOPPS, M D

CHICAGO

In a previous report¹ the general problem of delayed healing and disruption of wounds was discussed and experimental evidence was given to support the fact that hypersensitivity to catgut can be produced in animals by adequate antigenic stimulation. The experiments to be described in this paper were designed to evaluate the effects of such hypersensitivity on the reaction of tissues to catgut sutures and on the healing of surgical wounds repaired with catgut

MATERIAL AND METHOD

Eighty-eight rabbits were used in this study. Plain and chromicized catgut, sizes no 0 and no 1, were used throughout the experiments. In all operative procedures the technics commonly used in surgical practice were employed to maintain asepsis. Operative sites were carefully prepared by shaving, scrubbing with soap and water and thoroughly cleansing with a solution of 1 per cent iodine in 70 per cent alcohol. Laparotomies were done with the animals under pentobarbital sodium anesthesia. The incisions were paramedian and 8 cm long, extending 2 cm from the pubis. These wounds were carefully closed in three layers with no 0, plain, non-boilable catgut,² which had been thoroughly washed free of tubing fluid in several changes of sterile isotonic solution of sodium chloride. Abdominal wounds were covered with massive sterile dressings and a binder, which in most instances were left in position until the fourth postoperative day. A second type of operation was done in which single strands of catgut were implanted into the pectoralis major or the trapezius muscle of rabbits. An initial small cutaneous incision was made to expose the muscle. The catgut was implanted in the form of a loose loop, which was firmly tied, and the cutaneous incision (which did not directly overlie the catgut) was closed with metal wound clips. No dressing was applied. All biopsy specimens were fixed in Zenker's fluid, embedded in celloidin, cut into sections 10 to 16 microns thick and stained with hematoxylin and eosin.

EXPERIMENTAL STUDIES

In five series of rabbits, catgut was implanted into muscle as described. In these series were included 18 normal rabbits, 10 sensitized to sheep

serum, 19 sensitized to sheep intestine, 16 sensitized to catgut and 6 immunized against heterophile antigen. In all of these treated animals, with the exception of those immunized against heterophile antigen, precipitins to catgut had been demonstrated. Titers ranged from 1/20 to 1/640, with an average of about 1/100, by the antibody dilution method. From one to three strands of catgut were implanted at operation. Biopsies were made at intervals of from one to five days. A total of 142 such biopsy specimens was studied. Although considerable variation in the reaction of tissue to suture material was evident within each group, among the groups taken as a whole there was no significant variation in the reactions at one, two, three and a half or five days to either plain or chromicized catgut.³ Average reactions to catgut at two days are shown by the photomicrographs in figure 1.

From these results it appeared unlikely that allergic reaction to catgut was a significant factor in the pathogenesis of disruption of wounds. It was considered advisable, however, to produce abdominal wounds in animals sensitized to catgut and in normal animals, repair these wounds with catgut sutures and observe the course of their healing over a sufficient period to allow for disruption, if that was going to occur. This was done with 10 normal rabbits and 9 rabbits which had received multiple injections of a mixture of sheep serum and finely powdered sheep intestine over a period of two and one-fourth months. In the latter group antibodies to catgut and to sheep serum had been demonstrated. Abdominal wounds were produced as previously described and carefully inspected at four, seven and nine days postoperatively. One sensitized animal showed slight focal erythema of the margins of the wound, and another exhibited moderate induration about one of the sutures. In neither of these was there any apparent effect on the normal rate of healing. A third sensi-

From the Department of Pathology, University of Chicago.

1 Hopps, H C. The Role of Allergy in Delayed Healing and in Disruption of Wounds. I. Antigenicity of Catgut, Arch Surg, this issue, p 438.

2 Johnson & Johnson, "Ethicon."

3 Davis and Geck. 'Thermoflex' nonboilable, plain no 1 catgut. Johnson & Johnson 'Ethicon' nonboilable, plain no 0 catgut, Scannlin twenty day chronic no 1 catgut.

tized animal dislodged his abdominal dressing on the second postoperative day and traumatized the wound so that there was a partial separation of the skin. At nine days from each of these animals a biopsy specimen was taken through the entire thickness of the abdominal wall to in-

plasia, reaction to suture material, state of the sutures (decrease in size, fragmentation, etc.) edema and presence of fibrin. These were estimated in a rough quantitative fashion and tabulated. There were no significant differences in these points between the two groups and in all

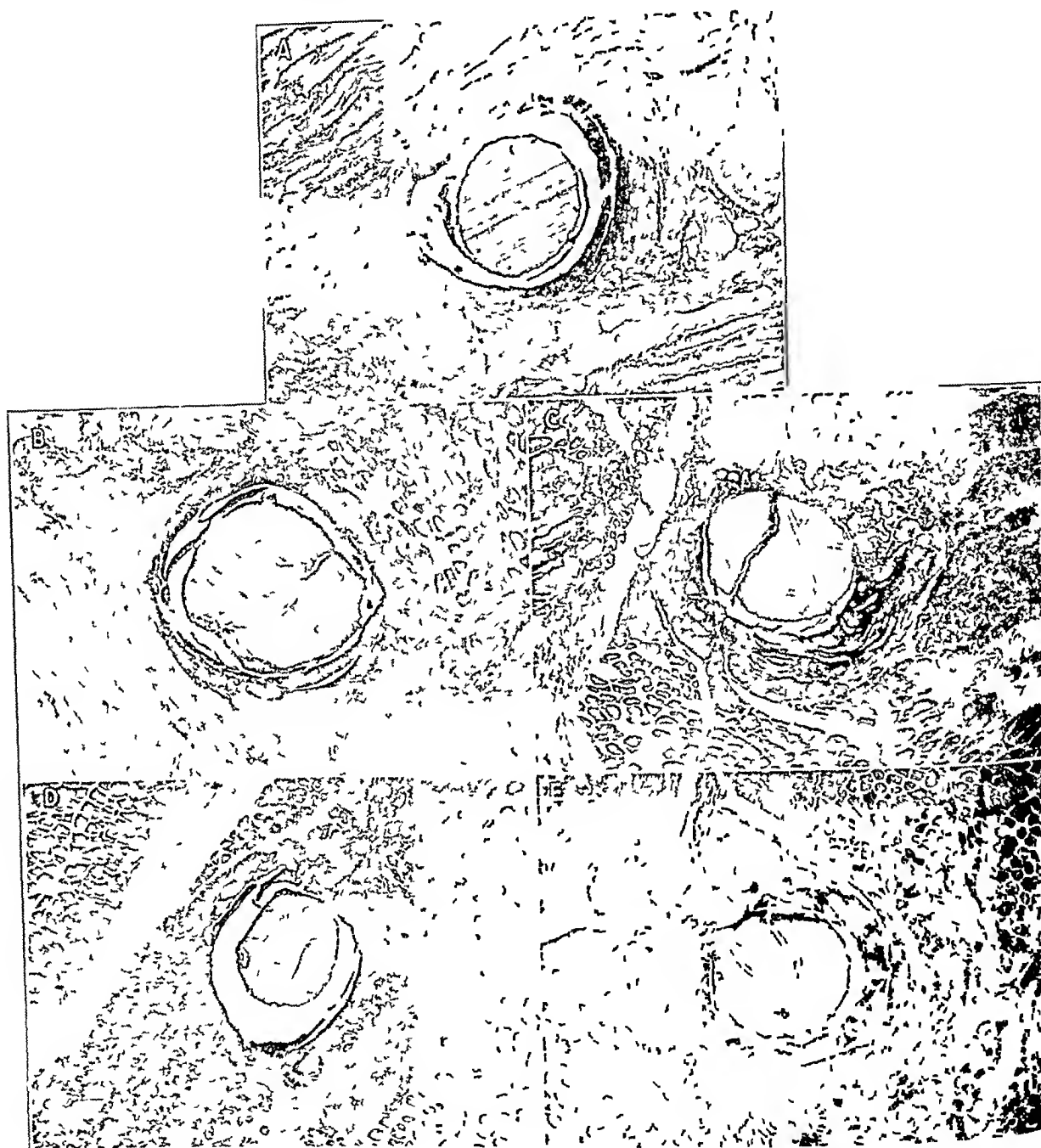


Fig 1—Photomicrographs ($\times 36$) showing average reaction to catgut sutures at two days in rabbits: *A*, normal; *B*, sensitized to sheep serum; *C*, sensitized to sheep intestine; *D*, sensitized to catgut; *E*, sensitized to heterophile antigen (stained with hematoxylin and eosin).

clude a portion of the incision and a portion of the suture material. At this time inspection was made of the peritoneal surfaces of the wounds and all appeared to be in a good state of repair. On histologic study of these tissues particular attention was given to general reactions (inflammatory, proliferative and degenerative), fibro-

animals the suture material was well preserved (fig 2). There was one change in 2 of the sensitized group, however, which was not present in any control animal, a change manifested by small, circumscribed granulomatous lesions, which closely resembled proliferating tubercles. One of the 2 sensitized animals showed a single such

lesion (fig 3), and the other exhibited several smaller but otherwise similar foci. No nidus of foreign material was evident in any of these tuberculoid nodules, nor did they resemble the occasional focal lesions which were definitely related to foreign body particles.

COMMENT

Catgut is antigenic, and sufficient sensitivity can be established to it so that a weakly positive Arthus reaction can be elicited from implantation of a strand of this material subdermally

which finely powdered catgut is treated with a 5 per cent solution of sodium chloride and constantly stirred for four hours at a p_H of 4.5 or 8 and the supernatant is concentrated ten times by evaporation from a cellophane bag and tested for protein. A faintly positive biuret reaction is obtained only after a delay of approximately thirty minutes. A situation analogous to this was brought out by Dr Tahaferro in his discussion of antigen-antibody reactions to metazoan parasites.⁵ He stated "The powdered cuticle of *Ascaris lumbricoides* var. *seium* is highly anti-

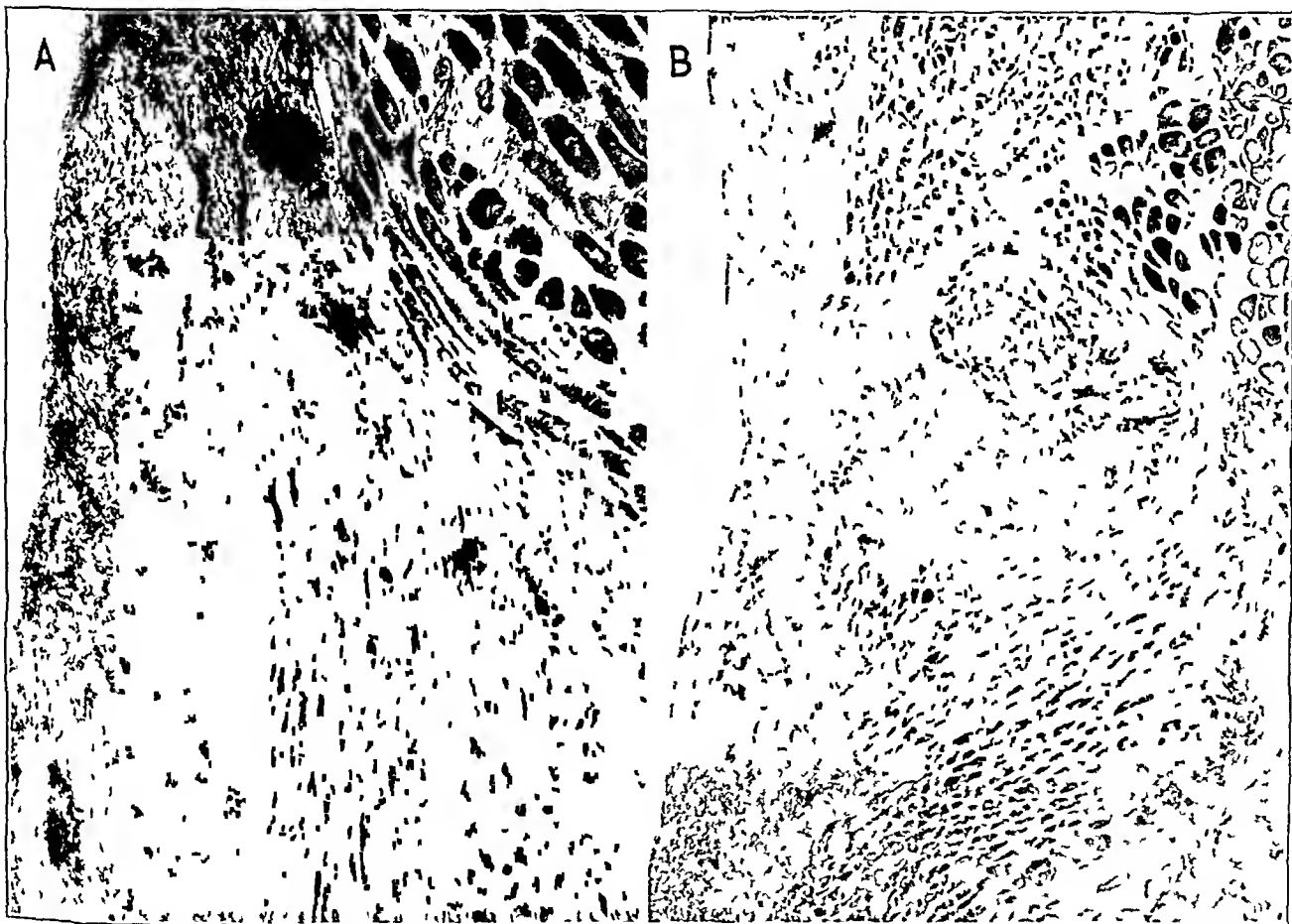


Fig 2—Photomicrographs ($\times 56$) of healing wounds nine days after operation in rabbits. *A*, normal, *B* hypersensitive to catgut. The free margin represents the peritoneal surface (stained with hematoxylin and eosin).

or into the anterior chamber of the eye.¹ In spite of this, however, disruption or appreciably delayed healing of wounds does not occur when animals sensitized to catgut are operated on and their wounds repaired with catgut sutures. The apparent paradox between the presence of humoral antibodies to catgut and the failure of tissues of specifically sensitized animals to give rise to allergic inflammation on contact with catgut probably rests on the fact that catgut is relatively insoluble. It is well known that catgut sutures may persist in the tissues for weeks or even months.⁴ This relative insolubility is well demonstrated by a simple experiment in

genetic and serum from infected rabbits exhibits a high anticuticle precipitin content but these antibodies do not react with the cuticle of the larvae [*in the tissues of sensitized animals*] because of the insolubility of the cuticle in the living worm.⁷

It has been stated by various observers that the absorption of catgut is greatly increased in

4 Feriz, H. Catgut and Collagen. *Surgery* **10** 326 1941.

5 Tahaferro, W. H. Antigen-Antibody Reaction in Immunity to Metazoan Parasites, *Proc Inst Med Chicago* **14** 358 1943.

certain persons Heyd⁶ spoke of a type of person in whom catgut may be completely dissolved before the tensile strength of the wound is sufficient to maintain closure Hinton⁷ referred to the "warning note by all authors as to the peculiar capacity of the tissues of some persons to digest catgut completely" Kraissl⁸ reported that of 56 cases of disruption of wounds in every case in which the appearance of the sutures was described (19) they were observed to be completely or almost completely digested Langston⁹ described a case of such digestion of

Howes¹⁰ stated that in the presence of fluids such as isotonic solution of sodium chloride or blood serum the tensile strength of catgut is moderately diminished and that in an inflammatory exudate catgut, either plain or chromicized, loses tensile strength rapidly However this may be, in rabbits with demonstrable hypersensitivity to catgut absorption of catgut sutures in the tissues is not increased appreciably during the critical period of healing of the wound This observation is substantiated by the recent studies of Vaccaro and Cabezas,¹¹ who demonstrated



Fig 3—Photomicrograph ($\times 56$) showing a tuberculoid lesion in a healing wound of a rabbit sensitized to catgut nine days after operation (stained with hematoxylin and eosin)

sutures in a patient who gave a positive reaction to a cutaneous test with catgut extract In a discussion of factors which determine the loss of strength of catgut when embedded in tissue

that in rabbits and guinea pigs which had been sensitized to sheep serum or catgut, absorption of catgut implanted into the peritoneal cavity was *delayed*

It may appear difficult to reconcile this fact with the demonstration that rabbits sensitized to catgut manifested a positive Arthus reaction

6 Heyd, C G Disruption of Abdominal Wounds *Ann Surg* 99 39, 1934

7 Hinton, J W Allergy as an Explanation of Dehiscence of a Wound and Incisional Hernia, *Arch Surg* 33 197 (Aug) 1936

8 Kraissl, C J Intrinsic Factors Altering the Absorption of Catgut, *Surg Gynec & Obst* 63 561, 1936

9 Langston, H T The Problem of Catgut Sensitivity and Its Relation to Wound Healing, *Ann Surg* 115 141, 1942

10 Howes, E L Factors Determining the Loss of Strength of Catgut When Imbedded in Tissue, *J A M A* 90 530 (Feb 18) 1928

11 Vaccaro, H, and Cabezas, V J Alergia al catgut y produccion de adherencias Estudio experimental y clinico, *Rev med de Chile* 70 750, 1942

to catgut implanted subdermally¹ It will be recalled, however, that such a reaction was slight and characterized principally by erythema It is logical to assume that the slight cutaneous reactions which were observed in the abdominal wounds of 2 sensitized animals, as previously described, represent a similar degree of allergic reaction and that the tuberculoid lesions described in the deeper tissues of several of the wounds also indicate an altered response to catgut by rabbits hypersensitive to catgut The allergic inflammatory reaction to catgut implanted into the anterior chambers of the eyes of specifically sensitized rabbits is somewhat different There the suture material is in a fluid medium and, according to Howes, susceptible to more rapid dissolution than could be expected in sterile solid tissue Although Hektoen and Carlson¹² showed that the aqueous normally contains few antibodies even in an animal with a high humoral antibody titer, any procedure by which large particles of foreign material are introduced into this chamber should afford sufficient trauma to allow for a considerable increase in permeability of the encapsulating membrane and a ready entrance of antibody protein

¹² Hektoen, L, and Carlson, A J On the Distribution of Antibodies and Their Formation by the Blood, *J Infect Dis* 7 319, 1910

It is possible that under certain conditions in which the solution of catgut sutures in tissues is greatly accelerated a significant allergic inflammatory reaction might result if the affected person were hypersensitive to catgut Under such circumstances, however, the hastened absorption of suture material with accompanying loss of tensile strength would represent the primary defect and would probably be sufficient basis in itself for disruption of the wound

SUMMARY AND CONCLUSIONS

In animals which are hypersensitive to catgut evidence of slightly heightened reaction of the tissues to catgut sutures has been observed

There is no appreciable difference between normal rabbits and rabbits sensitized to catgut in the rate of dissolution or digestion of catgut sutures during the critical period of healing of wounds

There is no significant difference between normal rabbits and rabbits sensitized to catgut in the healing of laparotomy wounds repaired with catgut sutures

The absence of significant allergic reaction to catgut in the wounds of animals sensitized to catgut is attributed to the relative insolubility of catgut sutures

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ROLE OF ALLERGY IN DELAYED HEALING AND IN DISRUPTION OF WOUNDS

III DELAYED HEALING AND DISRUPTION PRODUCED BY LOCAL ALLERGIC REACTION (AUER PHENOMENON)

HOWARD C HOPPS, M D

CHICAGO

Local anaphylaxis has been suggested as a mechanism which provokes disruption or delayed healing of surgical wounds. Catgut sutures have been considered the offending allergen in such instances. As a direct effect of antigen-antibody reaction within the wound, premature dissolution of catgut and/or increased inflammatory reaction have been postulated. In a preceding study,¹ evidence was presented to show that premature dissolution of catgut or significant inflammatory response does not occur in the tissues of specifically sensitized animals on contact with catgut, because of the relative insolubility of this material. The effect of local anaphylactic reaction within the tissues of a healing wound thus remains to be investigated. In order to determine its effect, a new mechanism was sought, one by which a local concentration of *soluble* antigen and specific antibody at the site of the healing wound could be effected.

Auer,² in 1920, first demonstrated that at the site of an early mild inflammatory reaction a massive severe inflammation could be superimposed by parenteral administration of a large dose of antigen to a specifically sensitized animal. He produced severe inflammatory reactions and necrosis in the ears of rabbits sensitized to horse serum by gently rubbing the ears with xylene and then injecting 10 cc of horse serum intraperitoneally. Auer described this reaction as "local autoinoculation of the sensitized organism with foreign protein" and attributed the resultant inflammatory response to a primary, local anaphylactic reaction. He expressed the opinion that this reaction was a variation of the Arthus phenomenon, differing from it, for one thing, in that "the sensitized animal reinjects itself where

there are inflammation and edema, providing that some of the antigen is circulating, the amount being so dilute that it is ineffective under ordinary conditions." In recent studies on the mechanism of the Arthus reaction, by Cannon and Marshall,³ it has been demonstrated that this phenomenon is related definitely to the presence of precipitins in the blood and that the intensity of such a local anaphylactic reaction parallels the precipitin content of the blood. If it is admitted that the phenomenon of Arthus and that of Auer are analogous, it becomes necessary to go one step further than Auer did in explaining the mechanism by which local anaphylaxis occurs. It must be assumed that not only is antigen concentrated locally in the area of primary inflammation, but antibody, from the blood, is concentrated there as well.

Inasmuch as a fresh surgical wound represents a focus of early acute inflammation, it was considered that under proper conditions circulating antigen and antibody might localize there. A quotation from the introductory paragraph of Auer's paper on local anaphylaxis is of special significance in this respect. "While testing the sensitiveness of a number of dogs which had been treated with horse serum some years previously, and employing heavy doses of horse serum for the reinjections, it was observed that a peculiar edema developed at the site of the operation wound in the inguinal region. This edema was noted about two days after the test and formed a fairly extensive, thick brawny mass of tissue."

It is generally accepted that disruption of the wound is more prone to occur when an abdominal operation is done in the face of preexisting infection, such as pelvic abscess or peritonitis. Although this increased incidence of breakdown of the wound may be in response to direct infection of the wound, the possibility of yet another mechanism appears. In the presence of a well localized infection, the patient may be assumed

From the Department of Pathology, University of Chicago

1 Hopps, H C. Role of Allergy in Delayed Healing and in Disruption of Wounds. II. Effect of Specific Sensitivity to Catgut on Reaction of Tissues to Catgut Sutures and on Healing of Wounds in the Presence of Catgut Sutures, *Arch Surg*, this issue, p 445

2 Auer, J. Local Autoinoculation of the Sensitized Organism with Foreign Protein as a Cause of Abnormal Reactions, *J Exper Med* 32 427, 1920

3 Cannon, P R, and Marshall, C E. Studies on the Mechanism of the Arthus Phenomenon, *J Immunol* 40 127, 1941

to have a rather high degree of immunity or sensitivity to the specific infectious agent and a high humoral antibody titer. As the result of operative manipulation of such a localized infectious lesion, an appreciable amount of dead or living bacteria and their products may be forced through the protective barrier of granulation tissue to enter the general circulation. Under these conditions all of the necessary requirements for the development of an Anker reaction would be fulfilled: (1) the surgical wound, providing a localizing lesion, (2) the chronic infection, stimulating a high humoral and

was produced, as demonstrated by strongly positive cutaneous reactions (Arthus) and by high precipitin titers of the serums, averaging 1:1,500 in either group, as determined by the antibody dilution method of Cannon and Marshall.

Abdominal operations were performed under strict aseptic precautions in the same manner as described in preceding experiments.¹ The abdominal wounds were parameedian and 8 cm long. They were carefully closed in three layers either with plain, no 0, nonboilable catgut² from which tubing fluid had been thoroughly washed—or with silk. Wounds were covered with massive sterile dressings and tight binders, which were left intact until the fourth postoperative day. Ten cubic centimeters of 0.35 per cent egg albumin or 10 cc of 35 per cent horse serum (in saline solution) was

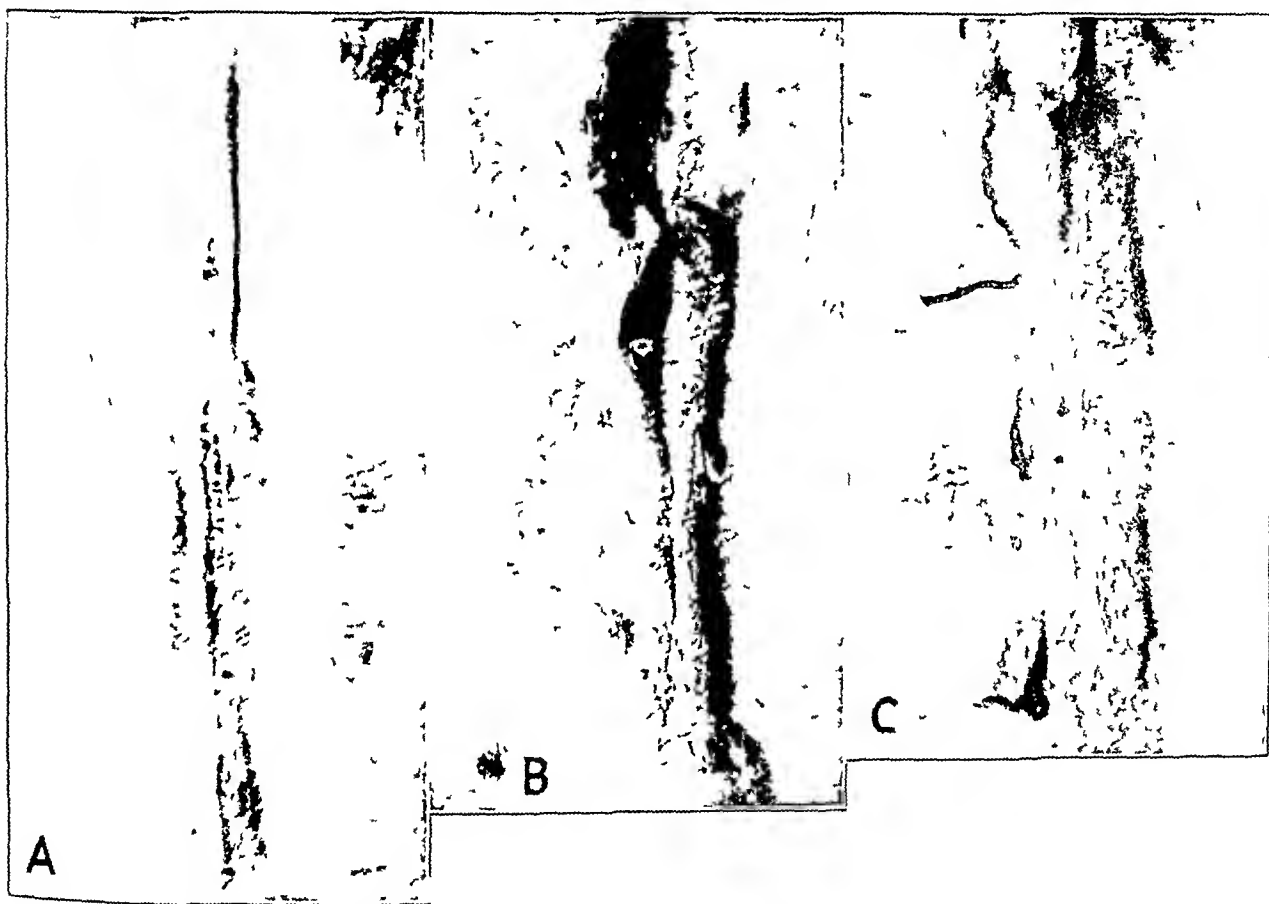


Fig 1—Photographs illustrating the gross appearance of abdominal wounds at seven days in (A) normal rabbit and (B and C) 2 rabbits sensitized to horse serum. Each animal received horse serum intravenously immediately after the operation. Note that for the animal in C silk was the suture material used. (An interrupted horizontal mattress stitch was used to close the cutaneous layer.)

tissue antibody titer, and (3) manipulation of the localized infectious process, allowing for the introduction of specific antigen into the blood stream. To test this hypothesis, the following experiments were done.

MATERIAL AND METHOD

Sixty-one rabbits were used in this study. Rabbits were sensitized to either horse serum or crystalline egg albumin by multiple intramuscular injections of these substances adsorbed on aluminum hydroxide gel, after the method of Hektoen and Welker,³ with additional subcutaneous injections of horse serum or 1 per cent solution of egg albumin. A high degree of sensitivity

was injected into the marginal vein of the ear over a period of fifteen to thirty minutes immediately after operation to specifically sensitized and to control animals.

Biopsy specimens were fixed in Zenker's fluid, embedded in celloidin and sectioned at 10 to 16 microns. Sections were stained with hematoxylin and eosin, and also with a combination of Bielschowsky's silver impregnation method with Hansen's modification of Van Gieson's stain for collagen.

4 Hektoen, L., and Welker, W. H. Precipitin Production in Rabbits Following Intramuscular Injection of Antigen Adsorbed by Aluminum Hydroxide, *J Infect Dis* 53:309, 1933.

5 Johnson & Johnson "Ethicon" suture.

EXPERIMENTAL STUDIES

Laparotomy wounds were made in 37 rabbits. Sixteen of these animals had been sensitized to horse serum and 15 to crystalline egg albumin in the manner described. Six were normal animals. Of these 31 sensitized animals, 25 received specific antigen intravenously after operation. The remaining 6 received foreign protein (egg albumin or horse serum) other than that to which they were hypersensitive. The 6 normal rabbits received egg albumin or horse serum also. Thus, within the control group of

hyperemia of the margins of the wound. Most of the animals of this group exhibited edema and hyperemia of the margins of the wound and a moderate degree of serosanguineous exudation. It is of special interest that, of the 3 animals whose wounds were repaired with silk sutures, in 1 separation of the upper layers of the wound developed and in another there was gaping of the margins of the skin (fig 1). In this group the reactions of the animals sensitized to horse serum and of those sensitized to egg albumin were essentially similar. The intensity of the reactions tended to parallel the precipitin titers

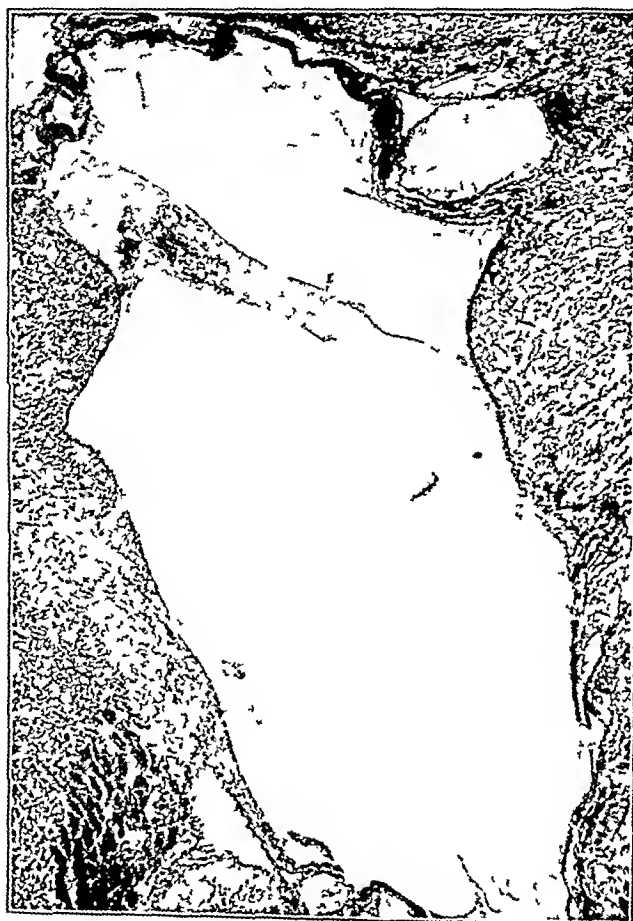


Fig 2—Photomicrograph ($\times 40$) showing the appearance of the margins of the wound (deep) at nine days in a rabbit sensitized to horse serum which was given horse serum intravenously immediately after the operation (Stained with hematoxylin and eosin)

12 rabbits any nonspecific effects attributable to a state of hypersensitivity or to the introduction of foreign protein could be determined.

Twelve of the sensitized rabbits receiving specific antigen died of anaphylactic shock. An additional animal was discarded from this series because of infection of the wound. Of the remaining 11 animals, in 2 frank separation of the upper layers of the wound developed (without actual evisceration) and 7 exhibited gaping of the margins of the skin. In 2 animals an untoward reaction was limited to induration and

of the serums, which varied from 1:960 to 1:1,920. Of 12 control animals, infection of the wound developed in 1 and another dislodged its abdominal dressing and traumatized the wound, with resultant partial separation of the cutaneous layer. In the remaining 10 controls, separation of the layer of skin developed in only 2, and over but a portion of the wound. These 2 animals did not exhibit the degree of edema and hyperemia seen in the specifically sensitized group, nor was there serosanguineous discharge from their wounds.

Nine days after operation, biopsy specimens were taken through the wounds at right angles to the plane of incision and the tissues prepared for microscopic examination. Tissues were carefully studied with special consideration of the following points: general reaction (inflammatory, proliferative and degenerative), degree of fibroplasia reaction to sutures, state of sutures (intact, fragmented, etc.), edema and presence and extent of deposition of fibrin. In 4 of the 11 sensitized animals which received specific antigen after

the intact portions of tissue. On examination of the area of incision under low magnification, the number of inflammatory cells appeared about the same in the two groups of animals. On closer scrutiny, however, it was seen that the types of inflammatory cells present differed significantly, the ratio of macrophages to fibroblasts was considerably greater in the animals into which specific antigen had been injected after operation. In biopsy specimens from this group, under high power magnification, fields were often

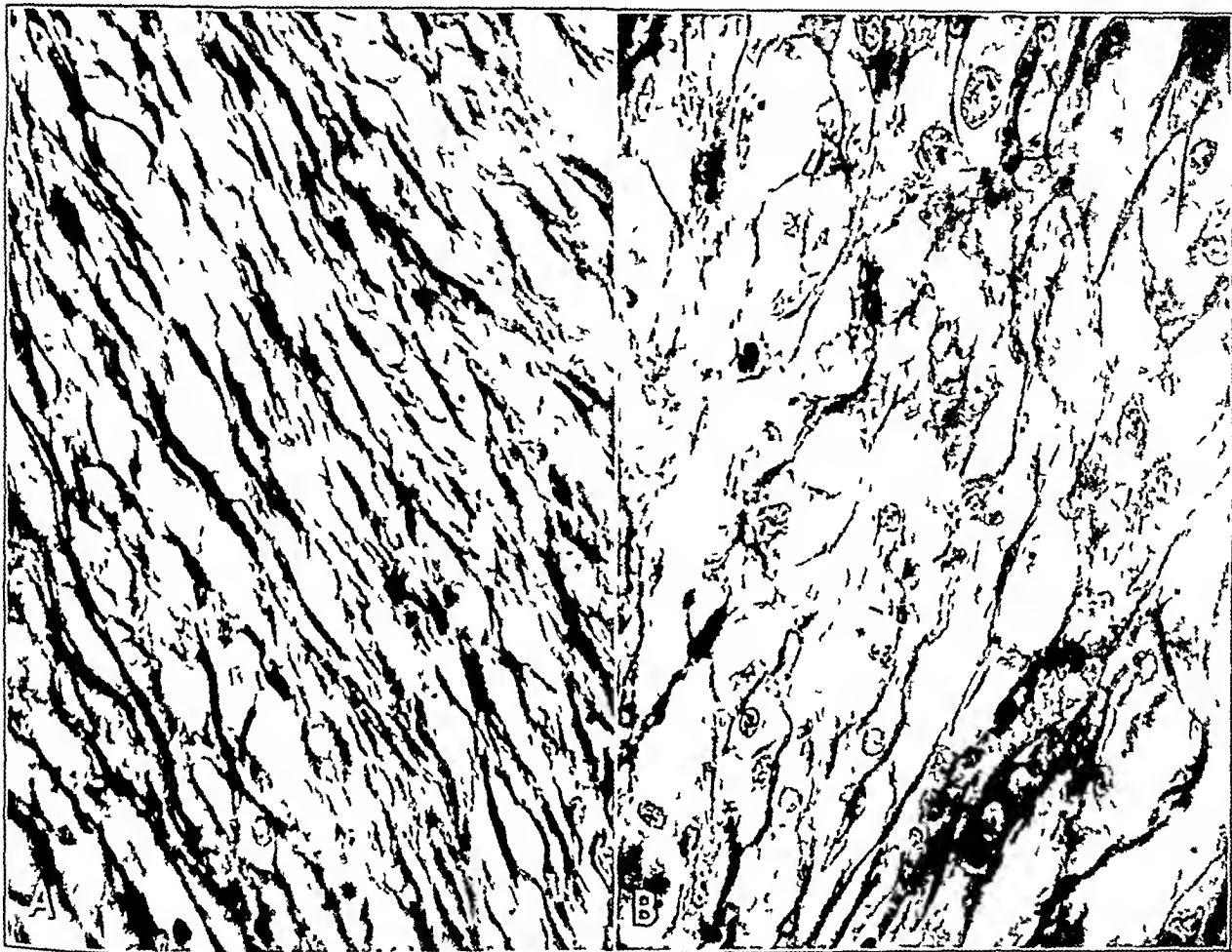


Fig 3—Photomicrographs ($\times 630$) of sections taken across the plane of incision of laparotomy wounds nine days postoperatively from (A) a normal rabbit and (B) a rabbit sensitized to horse serum. Both received horse serum intravenously immediately after operation. Note the sparseness of fine reticulum and the absence of collagen in (B), although macrophages are plentiful. This wound partially disrupted. (Stained with a combination of Bielschowsky's silver impregnation method with Hansen's modification of Van Gieson's stain for collagen.)

operation, there was evident frank separation of the margins of the wound in the deeper layers of tissue (fig 2). This was observed in none of the controls, although in 2 animals there was separation of muscle from subcutaneous tissue in a plane parallel to the surface of the skin. There was no significant difference between the two groups of animals in the reaction to the sutures or in the state of the sutures, and, surprisingly, no appreciable difference in the degree of general inflammatory reaction in the plane of incision or in the amount of edema present in

found directly in the line of incision in which not a single fibroblast could be seen, although macrophages were plentiful (this was nine days postoperatively). As a general rule, in the latter group of animals the reticulum was finer and sparser and there was much less collagen than was found in control animals (fig 3). This difference appeared sufficient to explain the structural weakness and the resultant disruption of wounds which were observed.

When biopsy specimens from this series of animals which had received foreign protein intra-

venously after operation were compared with those from a group of 19 animals which had been subjected to a similar operative procedure but which had not received foreign protein intravenously, it was observed that in the animals of the former group considerably more degenerative changes in skeletal muscle had occurred at the site of the laparotomy wound. There was waxy degeneration of many of the fibers, others exhibited necrosis and were in the process of being digested by macrophages. These changes were essentially similar in all the animals which had received either horse serum or egg albumin after operation, regardless of whether or not they had been previously sensitized to the injected protein. These changes did not appear to alter significantly the rate or quality of the healing of the wound and they were not associated, at nine days, with an acute inflammatory reaction.

Two other experiments were carried out for reasons which will be considered later. In each of these, rabbits sensitized to horse serum and to crystalline egg albumin were used. The method of sensitization and the degree of hypersensitivity were similar to those previously described. In the first of these experiments, 12 rabbits were used. Three of these were hypersensitive to horse serum and 3 to egg albumin, 6 were normal controls. Tiny loops of plain, no 0 catgut, thoroughly washed to eliminate tubing fluid, were implanted subdermally in the ventral surface of the abdomen. (Cutaneous surfaces had been carefully shaved the preceding day.) Immediately after this procedure 10 cc of 35 per cent horse serum was given intravenously to the 3 animals sensitized to horse serum and to 3 normal controls. The 3 animals sensitized to egg albumin and the remaining 3 normal controls received 10 cc of 0.35 per cent solution of egg albumin. Two of the 6 sensitized animals died of anaphylactic shock. In the remaining 4 there was no significant difference in the reaction to implanted catgut at twelve, twenty-four, forty-eight or sixty hours. In the second experiment a different sort of inflammatory agent was used, the undiluted tubing fluid from boilable catgut. Tubing fluid of boilable catgut is essentially similar in composition regardless of the type or brand of catgut selected. It consists, in major part, of homologs of benzene, such as toluene or xylene. It has been recently demonstrated by Jenkins and Dunham⁶ that this substance provokes a severe degree of inflammation on contact with tissues. Tubing fluid of boilable catgut in

0.1 cc amounts was injected intradermally into the ventral surface of the abdomen in 6 sensitized and 6 normal animals, which were then given an intravenous injection of horse serum or egg albumin in the same manner as described previously. Four of the 6 hypersensitive rabbits survived the injection of specific antigen. At twenty-four, forty-eight and sixty hours a significant difference was observed between the reactions of the sensitized animals and those of the control animals. In the control animals a fairly well circumscribed area of acute inflammation developed which on the average measured approximately 1.5 cm in diameter. A small area of central necrosis was present in most instances. In the sensitized animals, however, the area of inflammation was less well circumscribed and 50 to 100 per cent larger. Central necrosis was more extensive and less well defined. These observations demonstrate the potency of tubing fluid as an inflammatory agent and show that inflammation produced by such a substance will, under proper circumstances, provoke an Auer reaction, whereas catgut per se is relatively innocuous in this respect.

COMMENT

It has been demonstrated in the preceding section that the healing of laparotomy wounds is profoundly altered in rabbits previously sensitized in which specific antigen is reinjected postoperatively. In normal as well as in sensitized control animals which receive nonspecific foreign protein, laparotomy wounds heal without significant untoward reactions. In an interpretation of these observations, the most obvious explanation is that a local anaphylactic reaction plays a predominant part. With this, however, there are other possibilities to be considered.

Local Anaphylactic Reaction—Auer considered that local autoinoculation of the sensitized animal was accomplished by the passage of specific antigen into the inflammatory lesion as a complement of the edematous fluid which accumulated there and that in the case of an operative wound "the amount of foreign protein acting locally would be increased by the oozing of blood, serum, plasma and lymph into the wound from the severed blood and lymphatic capillary channels all of which contain the antigen." From more recent studies concerning the localizing action of inflammatory lesions,⁷ an additional

6 Jenkins, H. P., and Dunham, C. L. Irritant Properties of Tubing Fluids as a Factor in the Tissue Reactions Observed with Surgical Gut (Catgut), *Ann Surg* 118: 288, 1943.

7 Burrows, H. Some Factors in the Localization of Disease in the Body, New York, William Wood & Co., 1932. Fox, J. P. The Localization and Concentration of Blood-Borne Antibodies and Colloidal Dye in Areas of Inflammation of Various Ages, *J Immunol* 31: 293, 1936. Rigdon, R. H. Capillary

mechanism to explain local automoculation is suggested. It has been shown that acute inflammatory processes localize and concentrate such vital dyes as trypan blue, Chicago blue and Evans blue when given intravenously and that protein substances too, e. g., hemolysins, agglutinins and antitoxins, may be localized under such conditions. It appears from this that antigen and antibody, or products thereof, may be actively concentrated in areas of inflammation, in addition to any passive accumulation that may occur. Such local accumulation would provoke allergic inflammation of the type and degree illustrated by the Arthus reaction.

Catgut per se does not provide an adequate stimulus for local accumulation of antigen and antibody, as has been shown. This fact is in keeping with the observation that in sensitized rabbits into which specific antigen was reinjected postoperatively, the reaction to catgut sutures in the abdominal wounds was not significantly altered. It will be recalled that all catgut used was of the nonboilable variety and had been carefully washed free of tubing fluid in several changes of warm sterile saline solution before being used in animals. The effects of tubing fluid have been described, and the facts demonstrated that tubing fluid of boilable catgut is in itself a potent inflammatory agent and that inflammatory lesions produced by that substance can elicit an Auer reaction.

Direct or Indirect Effects of General Anaphylaxis—The profound effects obtained from the introduction of large amounts of specific antigen into sensitized rabbits is illustrated by the fact that in the experiments described 16 of 37 animals so treated died of anaphylactic shock. In the survivors, effects of impaired

circulation, toxic substances in the blood or metabolic disturbances, such as might result from extensive necrosis of the liver, described by Hartley and Lushbaugh,⁸ may well have influenced the healing wound adversely. It is to be noted, however, that except in 2 or 3 instances these animals appeared to have recovered from any ill effects of this treatment within twenty-four hours or less.

Local Formation of Antibodies—It has been observed that the degree of inflammation present at nine days in healing wounds of sensitized animals into which specific antigen has been reinjected does not differ appreciably from that of control animals in which healing of the wounds is satisfactory. This fact would tend to discredit local allergic inflammation, of the type described by Auer, as the principal mechanism responsible for the decreased tensile strength exhibited by the wounds of specifically sensitized animals after reinjections. The major abnormality in these wounds, and one which appeared adequate to explain their lack of tensile strength, was the relative sparsity of fibroblasts and collagen, as has been illustrated in figure 3. Since the number of potential fibroblasts in these wounds was within normal limits, it was concluded that a failure of normal maturation of macrophages into fibroblasts had occurred. To explain this phenomenon, two possible mechanisms were considered: (1) Some toxic substance and/or abnormal catabolic products had caused injury to macrophages so that their development was altered, or (2) these macrophages were in the process of forming antibodies and, as a result of this internal stimulus, failed to develop into fibroblasts. That macrophages can form antibodies at a site of local inflammation has been well demonstrated by Cannon and Sullivan⁹ and by Hartley¹⁰. In an area of inflammation in which antigen is introduced, there seems little doubt that the macrophages present would engage in the process of forming antibodies. It may be that macrophages retain their status as macrophages so long as they are called on to perform duties which they only, as progenitors of fibroblasts, are able to perform. When they have become fibroblasts, their ability to phagocytose and to produce antibodies is markedly diminished or lost altogether. Apparently the

Permeability in Areas of Inflammation Produced by Xylene, *Arch Surg* **41** 101 (July) 1940. Rigdon, R. H. Localization of Staphylococci in Areas of Inflammation Produced by Xylene, *ibid* **41** 879 (Oct) 1940. Rigdon, R. H. Observations on Capillary Permeability in Areas of Inflammation Produced by Staphylococci, *Surgery* **9** 436, 1941. Rigdon, R. H., and Haynes, A. Observations on Capillary Permeability and Inflammation in the Skin of Sensitized Rabbits, *J Lab & Clin Med* **27** 598, 1942. Rigdon, R. H., Ewing, F., and Tate, A. Effects of Infra-Red Irradiation on the Tissues of the Rabbit, *Am J Path* **19** 517, 1943. Rigdon, R. H. Localization and Concentration of Staphylococcus Antitoxin in Areas of Rabbit's Skin Treated with Ultraviolet Irradiation, *Am J Roentgenol* **50** 101, 1943. Rigdon, R. H., and Curl, H. Effect of Roentgen Irradiation on Capillary Permeability and Inflammation in the Skin of a Rabbit, *ibid* **49** 250, 1943. Rigdon, R. H. Localization and Concentration of Staphylococcus Antitoxin in Areas of Rabbit's Skin, *J Lab & Clin Med* **27** 37, 1941. Menkin, V. Dynamics of Inflammation. An Inquiry into the Mechanism of Infectious Processes, New York, The Macmillan Company, 1940.

8 Hartley, G., Jr., and Lushbaugh, C. L. Experimental Allergic Focal Necrosis of the Liver, *Am J Path* **18** 323, 1942.

9 Cannon, P. R., and Sullivan, F. L. Local Formation of Antibody by the Skin, *Proc Soc Exper Biol & Med* **29** 517, 1932.

10 Hartley, G., Jr. The Local Formation of Antivaccinal Antibodies by the Skin, *J Infect Dis* **66** 44, 1940.

incentive to remain macrophages and form antibodies is stronger than the incentive to mature into fibroblasts and form collagen as a process of the healing of wounds. The probable course of events in wounds which heal under such conditions is illustrated in figure 4.¹¹

It may be recalled that in all animals which received foreign protein intravenously after operation, regardless of specific sensitivity, certain degenerative changes in the tissues of the wounds were more pronounced than in control animals

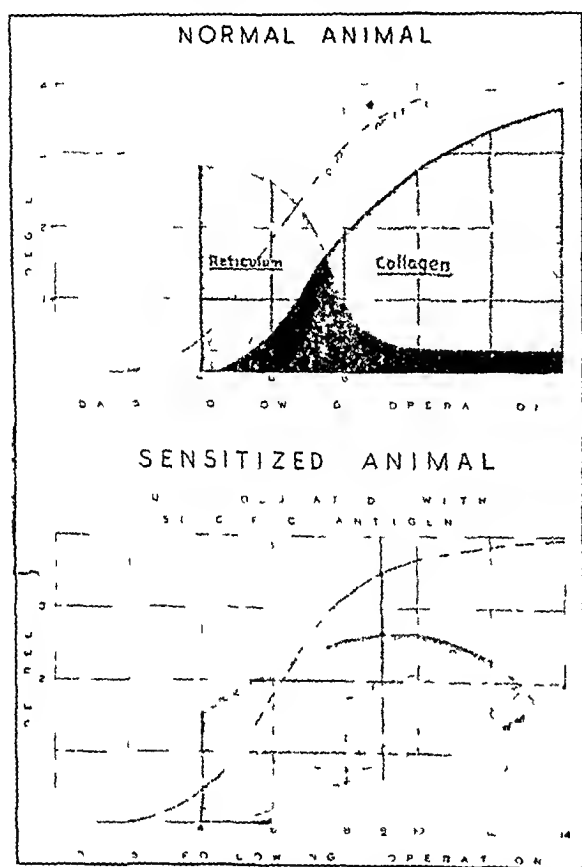


Fig 4—Chart illustrating the course of events during the healing of a wound in a normal animal, slightly modified from data published by Hunt. In the normal animal, tensile strength closely follows the upper boundary of the area of collagen. In the sensitized animal autoimmunized with specific antigen, the course of healing of the wound has been postulated on the basis of histologic observations at nine days only. These postulated changes are similar to those observed by Hunt¹¹ and others in the healing wounds of scorbutic guinea pigs, in which the major defects were failure in the formation of collagen and immaturity and poor holding power of the intercellular substance.

which did not receive foreign protein after operation. It appears that these changes in the tissues were not due to an immediate local anaphylactic reaction but were dependent only on the intravenous administration of an antigen which af-

forded, through the mechanism of local autoimmunization, the condition necessary for the formation of antibodies locally within the wound.

A possible explanation for the differences between the healing processes of sensitized animals which received specific antigen and those of animals which received nonspecific antigen rests on the fact that in the former group the animals had been previously prepared with specific antigen and were thus able to form antibodies more efficiently and at a faster rate. This phenomenon of specific anamnesis is discussed in a recent work by Cannon.¹² Such a reaction provides for a considerably greater stimulus for the production of antibodies in specifically sensitized animals and would afford a greater stimulus for the macrophages in the healing wounds of these animals to remain macrophages, rather than to mature into fibroblasts.

The clinical significance of this mechanism is probably not great, however, instances in which all of the factors necessary to bring about this mechanism are present certainly occur, and in such instances a local allergic reaction of the type described may act to produce delayed fibroplasia and disruption of the wound.

As a precautionary measure against such a reaction it is suggested that when abdominal operations are performed in the presence of chronic abdominal inflammatory lesions these lesions should be carefully protected from any trauma or, if their removal is desired, they should be "isolated" initially by means of clamps or ligatures. Such abdominal wounds should be thoroughly reinforced with nonabsorbable sutures and abdominal binders in order that the wounds may retain their initial "mechanical" strength for a longer period than is ordinarily required.

SUMMARY AND CONCLUSIONS

Local allergic reaction at the site of a surgical wound will delay healing and encourage disruption.

The mechanism of such delayed healing appears to rest in a failure of the maturation of macrophages, with resultant failure in the production of the reticulum and collagen.

There are several possible explanations for this mechanism, which is of clinical significance in certain cases in producing disruption of wounds.

Prof Paul R Cannon, of the Department of Pathology, gave valuable suggestions.

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¹¹ Hunt A H. The Role of Vitamin C in Wound Healing. *Brit J Surg* 28:436, 1941.

¹² Cannon P R. Antibody Production and the Anamnestic Reaction, *J Lab & Clin Med* 28:127, 1942.

PROGRESSIVE GANGRENE IN AN OPERATIVE WOUND

DONALD W. LEONARD, M.D.

CAMBRIDGE 2 1

The object of this article is to report a case of extensive destruction of the skin and the subcutaneous tissue in an operative wound closed after a routine removal of a gangrenous appendix and to discuss the observations already reported in medical literature regarding this rare but definite clinical entity. The case to be described is from the Mary McClellan Hospital, service of Dr. Denver M. Vickers and it is through Dr. Vickers' cooperation that this report is made possible. All surgical procedures were carried out under his direction or by him personally and his recollection of a similar account in the literature led to the finding of the first useful understanding of the problem.

Necrosis of a wound as a postoperative complication has been described enough in medical periodicals to be established as a definite entity with a definite mode of progression. Its appearance, as will be shown, is an indication for surgical intervention, as urgent as that for the operation which preceded it. Satisfactory treatment has been shown to depend on the recognition of this fact, inasmuch as the complication has never been known to yield to the measures ordinarily applied to the simple infections of wounds which it at first resembles. Failure to be aware of the possibility that such a postoperative situation can arise and consequent failure to profit by the experience of others may permit the ulceration to reach a considerable size.

In the course of the futile orthodox treatment of our patient a search of the literature was made without a clear idea of just what to look for. An article by Cullen published in 1924 was found to contain a complete description of a case with an excellent colored drawing, which might have served equally well as an illustration of our problem. This apparently was the second record of a case and began the chronologic list of reports later discovered, each article usually containing a description of a single case. The vital importance of these references in the satisfactory treatment of our patient and the complete absence of information in most textbooks seem to justify the publication of further observations from our experience and a review of the conclusions set forth by other surgeons.

CLINICAL OBSERVATIONS

The complication under discussion begins characteristically a week or more after operation and at a time when the sutures may have been removed from an apparently well healed incision. The first sign of trouble is a puffiness of the wound, giving evidence of a subcutaneous accumulation of fluid, as it does in many other instances when there is a collection of serum or pus resulting from exudate in tissue or infection. With this sign the most conservative treatment calls for a separation of the firmly united edges of skin at some point to allow the escape of the fluid. A small cavity is left, as is to be expected, but the whole situation to this point does not suggest anything too unusual. However, when a thinning of the entire scar and a separation of the edges by necrosis occur, it becomes obvious that a serious complication has developed, unchecked by the usually adequate drainage.

At this point, according to the published reports and to our own observations, the seriousness of the problem should be recognized and radical excision of the entire ulcerating area done. No writer has yet escaped this conclusion, but it is also true that in practically every instance in which this gangrenous ulceration has appeared it has been so unexpected that it has progressed far beyond this stage before the attending surgeon has felt justified in entering the healthy surrounding tissue with a knife unavoidably contaminated by this grossly septic lesion. Delay has caused further spread in all directions, faster longitudinally but always characterized by advancing necrosis of cutaneous margins, which become blackened into a drying slough floating on a gangrenous mass of subcutaneous fat honeycombed with purulent fluid and attached to surrounding skin, which shows for a variable distance a purple induration that seems to be the location of whatever pain the patient experiences. With all of this, in spite of wide extension, there is almost no systemic reaction other than that of the exhausting anxiety due to the inexorable advance of the process, which the patient can see as clearly as does his physician.

Summary of Cases Reported

Source of Ulceration	Patient		Date of Operation	Result	Author
	Age	Sex			
Appendectomy	50	M	9/28/22	Recovered	Cullen, 1924
Appendectomy	53	M	12/23/24	Recovered	Alexander, 1926
Appendectomy	64	M	12/18/25	Recovered	Brewer and Meleney, 1926
Appendectomy	39	M	11/24/26	Recovered	Gillespie, 1928
Appendectomy	34	M	5/24/27	Recovered	Cole and Heideman, 1929
Appendectomy		M	2/ /27	Recovered	Lynn 1931
Appendectomy	62	M	6/ /29	Recovered	Lynn, 1931
Appendectomy	52	M	10/16/29	Died	Liedberg, 1935
Appendectomy	32	M	10/20/30	Recovered	Baker and Terry, 1932
Appendectomy	54	M	1930	Recovered	Hellstrom, 1930
Appendectomy	35	M	1/ /31	Recovered	Meleney, 1931
Appendectomy	45	M	6/17/31	Recovered	Horsley, 1932
Appendectomy	62	F	8/11/31	Recovered	Meleney, 1933
Appendectomy	62	M	8/15/31	Recovered	Scotson 1933
Appendectomy	57	F	2/ 5/35	Recovered	Willard, 1936
Appendectomy	46	M	12/ /39	Died	Callam and Duff 1941
Appendectomy	49	F	11/ /34	Recovered	Blaxland, 1935
Appendectomy	62	M		Recovered	Ballin (Freeman, 1930)
Appendectomy		M		Recovered	Shipley, 1928
Appendectomy	62	F		Died	Vohnout, 1938
Appendectomy	45	M		Recovered	Poerschle 1938
Appendectomy	32	M		Recovered	Brewer and Meleney, 1926
Appendectomy	48	M		Recovered	Moschowitz (Brewer, 1926)
Appendectomy		F		Recovered	Meleney, 1935
Appendectomy	38	M		Recovered	Mayeda 1926
Appendectomy	38	M			Gordon, 1928
Appendectomy	70	M		Died	Mitchell (Lynn, 1931)
Appendectomy	32	M		Recovered	Terry (Lynn, 1931)
Appendectomy	37	M			Clinton 1926
Appendectomy	35	F			Porter 1926
Appendectomy					Warfield 1927
Appendectomy	62	M		Died	Carol, 1932
Thoracotomy	62	M	9/ /19	Died	Blaxland, 1935
Thoracotomy	62	M	6/29/30	Recovered	Patterson 1932
Thoracotomy	36	M	10/22/30	Died	Poate 1930
Thoracotomy	44	F	5/17/33	Recovered	Santy, 1936
Thoracotomy	54	M	1933	Recovered	Callam and Duff, 1941
Thoracotomy	44	M	2/13/34	Recovered	Stewart Wallace 1935
Thoracotomy	60	M		Recovered	Tavernier (Tixer and Pollos-son 1936)
Thoracotomy	54	M		Recovered	Ballin (Freeman, 1930)
Thoracotomy	48	M		Died	Brunsting, 1930
Thoracotomy	64	M		Recovered	Christopher 1924
Ruptured peptic ulcer	57	M	10/30/32	Recovered	Meleney, 1933
Ruptured peptic ulcer	57	M	6/ 5/33	Recovered	Scotson 1933
Ruptured peptic ulcer	44	M		Recovered	Cox 1936
Axillary abscess	25	F	2/ 6/31	Recovered	Holman, 1935
Axillary abscess	20	F	9/ 1/33	Recovered	Holman 1935
Axillary abscess	25	M	3/30/34	Recovered	Hirshfeld 1939
Inguinal abscess		M	10/ /25	Died	Meleney 1935
Inguinal abscess	8	M	1930	Recovered	Ballin and Morse 1931
Inguinal abscess	33	M	2/21/31	Recovered	Horsley, 1929
Abdominal wall abscess	55	M	5/30/08	Recovered	Luckett, 1909
Abdominal wall abscess		M	1/ 5/27	Recovered	Shipley, 1928
Hepatic abscess	63	F			Brewer and Meleney, 1926
Hepatic abscess					Tavernier (Tixer and Pollos-son, 1936)
Pelvic abscess		F	10/ /27	Died	Meleney, 1935
Pelvic abscess	46	F			Borell 1924
Hysterectomy	42	F		Recovered	Meleney, 1935
Hysterectomy		F		Recovered	Meleney, 1935
Cecostomy	63	F	12/ /31	Recovered	Meleney, 1933
Cecostomy					Delmas 1937
Gastroenterostomy	45	M		Recovered	Tixer and Pollosson 1936
Gastric resection	21	M		Recovered	Constantinescu, 1938
Cholecystectomy	39	F	3/27/29	Died	Freeman 1930
Peritoneal abscess		F		Recovered	Meleney, 1935
Rectal cancer	54	F		Died	Pergola and Rosenfeld 1935
Ventral hernia	64	F	1920	Recovered	Ballin and Morse 1931
Mammary abscess	35	F	6/16/26	Recovered	Probst and Seelig, 1928
Intussusception	67	M	12/14/27	Recovered	Horsley, 1929
Pilonidal sinus	28	M	9/ /37	Recovered	Hirshfeld 1939
Epididymal abscess	18	M		Recovered	Ballin (Freeman, 1930)
Pelvic exploration	42	F	2/ 6/31	Died	Holman 1935
Pustule on leg	43	M	7/ /34		Holman, 1935

Summary of Cases Reported—Continued

Source of Ulceration	Patient		Date of Operation	Result	Author
	Age	Sex			
Appendectomy *	45	M		Recovered	Stieh (Liedberg, 1936)
Appendectomy *	40	M		Recovered	Grauhahn (Liedberg, 1936)
Appendectomy *	50	M		Recovered	Brown (Liedberg, 1936)
Appendectomy *	11	F		Recovered	Hohmeier (Jaeger, 1938)
Appendectomy *	56	M		Died	Kappis, 1932
Appendectomy *	67	M		Recovered	Syme and Bryce, 1936
Appendectomy *	49	M		Recovered	Coakley and Klein, 1936
Appendectomy *	58	M		Recovered	Phillipowicz, 1936
Appendectomy *	50	M		Recovered	Syme, 1936
Appendectomy *	45	M		Recovered	Carroll, 1938
Appendectomy *	44	M		Died	Suss, 1937
Appendectomy *	48	M		Recovered	Wolanski, 1939
Appendectomy	60	I	4/30/39	Died	Dodd, Heekes and Geiser, 1941
Appendectomy	69	F	7/14/42	Died	Davison Sarnat and Lampert, 1944
Thoracotomy *	58	F		Recovered	Hieken, 1935
Thoracotomy *	47	F		Recovered	Brandberg, 1937
Ruptured peptic ulcer	43	M		Recovered	Duemling and Elston (Liedberg, 1936)
Ruptured peptic ulcer *	57	M		Recovered	Nightingale, 1934
Ruptured peptic ulcer *	77	M		Died	Wachulewski, 1939
Inguinal abscess *	4	M		Recovered	Ballin and Morse, 1931
Inguinal abscess *	74	I		Died	Wachs, 1937
Abdominal wall abscess *	52	M		Died	Krecke (Kappis, 1932)
Abdominal wall abscess *	76	M		Recovered	Oudnovskaja (Kappis, 1932)
Subphrenic abscess *	42	M		Died	Wachs, 1937
Umbilical abscess *	21	F		Died	Wachs, 1937
Pelvic abscess *	29	F		Died	Schlink and Thomson, 1935
Intestinal obstruction	67	M		Recovered	Dodd, Heekes and Geiser, 1941
Cholecystectomy *	44	I		Recovered	Kueppers, 1935
Cholecystectomy *	67	M		Recovered	Wakeley and Willway, 1937
Cholecystectomy *	58	F		Recovered	Tamman (Liedberg, 1936)
Herniotomy *	64	F		Recovered	Tennant (Freeman, 1930)
Herniotomy *	63	M		Died	Stohr and Nederland, 1935
Mammary abscess *	32	I		Recovered	Liedberg, 1936
Prostatectomy	60	M	7/10/39	Died	Dodd, Heekes and Geiser, 1941
Sympathectomy on thigh *	50	M		Recovered	Kappis, 1932
Abscess of tibia *	29	F		Died	Diebold, 1934
Pustule on leg *	72	M		Died	Kappis, 1932
Hand infection *	26	M		Recovered	Wachs, 1937
Varicose ulcer *	66	F		Recovered	Wachs, 1937

* Foreign references cited by Dodd, Heekes and Geiser, 1941, and included in their bibliography

PREVIOUS REPORTS

Accumulated experience will not give the surgeon much practical aid in reaching a decision about the cause of this complication, which spreads with such dramatic speed while he watches it. Reports of cultures are confusing, because many of the organisms isolated are of the usual varieties and it is impossible to understand why this lesion differs from others from which the same organisms are isolated. An amebic infection, apparently proved to be present in the cases of Cole and Heideman, or the synergistic bacterial combination discussed by Meleney in 1931 may appear to be attractive possibilities, but whether any of the varied techniques employed or the chemicals recommended have any special virtue has not been determined because of the lack of material. In reading one is certainly confronted with an enumeration of the standard methods of treatment for infection

of wounds that have definitely failed until excision was done. The successful healing of the lesions discussed in the literature with the application of certain theoretically correct chemicals after excision appears to have made persons enthusiastic who have ignored the possibility that the ulceration may heal spontaneously after the gangrenous advance has been stopped. It can also be correctly assumed that the failure of any chemical agent to stop the advance of the gangrenous process does not indicate that it is necessarily ineffectual against the unknown etiologic agent. It may rightly be assumed that it merely fails to reach the advancing margin until after the latter is uncovered by excision.

Thus a reference to literature creates a confusion which, by contrast, makes the simplicity of excision more evident. All the cases together furnish indirectly the proof that excision is urgently needed as soon as these characteristic

developments appear in a postoperative wound. The conditions for which the operations were done in the recorded cases of postoperative gangrenous ulceration are widely varied, but each author has had the same urge to share the experience and the lesson he learned from it. A study of the details in these reports justifies some question as to whether or not all of the lesions conform to the classic picture, but for a statistical study all of the 112 examples from the literature may be listed in a table, which is an

similar simple calculation it is discovered that in nearly 42 per cent of the cases the gangrenous ulceration followed operation for appendicitis and that in the rest it occurred after 31 different surgical procedures, of which thoracotomy for empyema dominated, with an incidence of a little over 10 per cent of the total. In 101 cases in which the age was given it is observed that whereas the youngest patient was 4 years old and the oldest was 77 in the cases in which ulceration followed various initial surgical operations as well as in

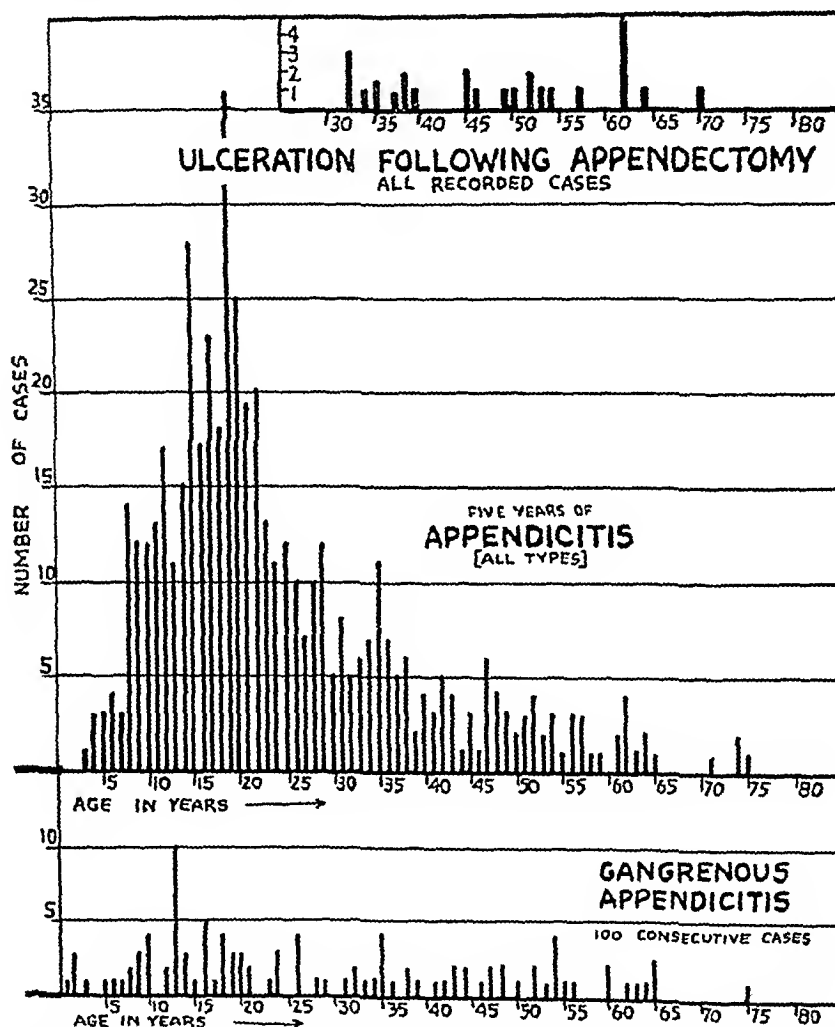


Fig 1—Comparison of the age distribution of cases of simple appendicitis, gangrenous appendicitis and ulceration following appendectomy. The last group appears well beyond the peaks of the curves for the other two and gives basis for the inference that the development of postoperative gangrenous ulceration in the wound depends on factors other than those related to the appendicitis itself.

expansion of similar summaries presented by Stewart-Wallace and Holman in 1935 and Dodd, Heekes and Geiser in 1941 (table).

From the information in the summary of the cases in the literature it is possible to make several interesting generalizations about the gangrenous ulceration although incomplete data in many cases make it necessary to use only a part of the total number. Thus it is observed that 108 reports stated the sex of the patient but that in 68 per cent of these it was male. By a

the smaller group in which it followed appendectomy, there was a rather uniform distribution of patients between the ages of 30 and 65 years.

Inasmuch as these figures indicate that postoperative gangrenous ulceration seems to follow appendectomy with greatest frequency, it is interesting to speculate about a possible relationship and to compare the age distribution, for one thing, with that for appendicitis (fig 1). In The Mary McClellan Hospital for a five year period it will be noted that the age of greatest

incidence of appendicitis of all types is definitely between 10 and 30 years. This conclusion is reached from inspection of figures from this hospital, but it is equally true of other tabulations of the same kind and may be accepted as a universal fact. The ulceration under consideration seems therefore to be related to other factors than those of appendicitis itself or the chance infection of the postoperative wound. However, in a tabulation of the age incidence of gangrenous or perforated appendicitis and of ulceration following appendectomy is made (fig 1) a wider distribution through the years is shown for the former and a relatively higher percentage of older patients appears to have had the latter, more severe complication. This suggests that some individual tissue susceptibility may appear in the later years of life after a septic surgical operation.

ulceration instead of merely a temporary delay of healing until the tissues immunize themselves against septic discharges. If it can be assumed that certain persons in the later years of life lack the power to produce immunity of the tissues and that then lack is more pronounced in the winter months, a warning of potential difficulty may be accepted, especially if this combination occurs in a male patient. The recognition of the possibility may lead to a more prompt adoption of radical treatment. The argument that the condition is rare does not obviate the tragic reality of the distress when the exceptional case appears.

To draw conclusions from a relatively small series may be a questionable procedure. No other method presents itself because even though many authors have remarked that other cases have been observed this supposed larger num-

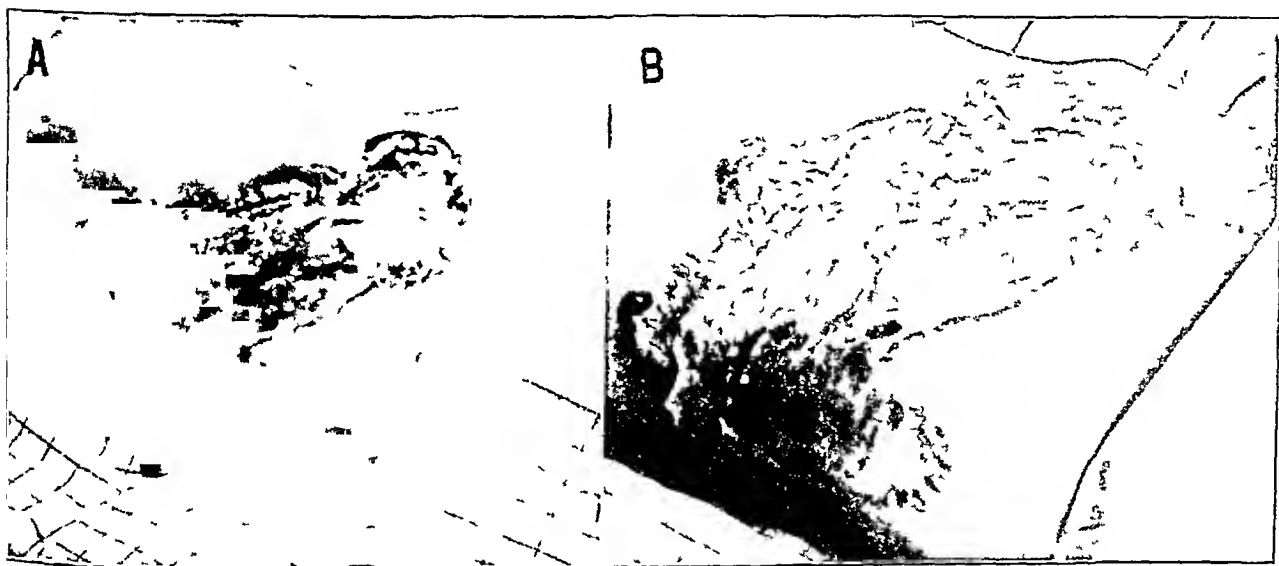


Fig 2—A, photograph of necrosis of an operative wound sixty-two days after operation and eight days after first excision of the necrotic margins with a high frequency cutting current. At the time of the excision short strokes were made at right angles to the margin and extending into the surrounding red induration, which was not removed. In the eight days following the first excision further necrosis appeared except along most of the lower margin and in two places on the upper margin. A second excision was done on the day of this photograph. B, photograph of the ulcerated area seventy-two days after the operation and ten days after the last excision. During the interval sulfathiazole powder was dusted on the granulating area every other day. It can be seen that active advance was stopped except at three points on the upper margin, which appear black with additional necrosis. Local excision at these three locations was done on the day of this photograph.

Further analysis of the cases in the literature in which the month of the operation was stated demonstrates that 66 per cent of the complications followed operations done in "winter months," from September to February, inclusive. A similar consideration of the cases in which gangrenous ulceration followed appendectomy leads to the fact that 69 per cent of these operations were done in the same winter months.

These observations of age incidence and seasonal distribution furnish material for a partial explanation of the situation which on certain occasions results in rapid gangrenous

ber of unrecorded cases cannot be used for tabulation.

TREATMENT

To the list of cases in the literature is now added 1 more. Our patient was a man of 56 who was operated on for a gangrenous appendix on Jan 24, 1943. The case therefore conforms to the pattern for potential trouble in regard to age, sex and season. This cannot be assumed to be the only case of its kind in the last few years. It can, however, be considered to be the only available instance of the complication that illustrates the failure of some of the sulfonamide

drugs and the success of repeated conservative excisions with the electrosurgical unit in contrast to the massive excisions previously advocated (figs 2 and 3). At the time when treatment by excision was finally undertaken, the usual local remedies, including drainage, diluted solution of sodium hypochlorite U S P, sulfanilamide, hydrogen peroxide, sodium perborate, ultra-violet radiation and zinc peroxide, had been tried without even a momentary arrest of the

while this was being used locally the patient was receiving sulfathiazole by mouth at the moderate rate of 1 Gm every four hours. If it is assumed that this dose gave sufficient concentration in the blood stream and that the advance of the process was not thereby stopped, it will be logical to assume that the circulating blood had been cut off before it reached the active margin which was undergoing necrosis and that the concentration was not effective in the protection of the tissue

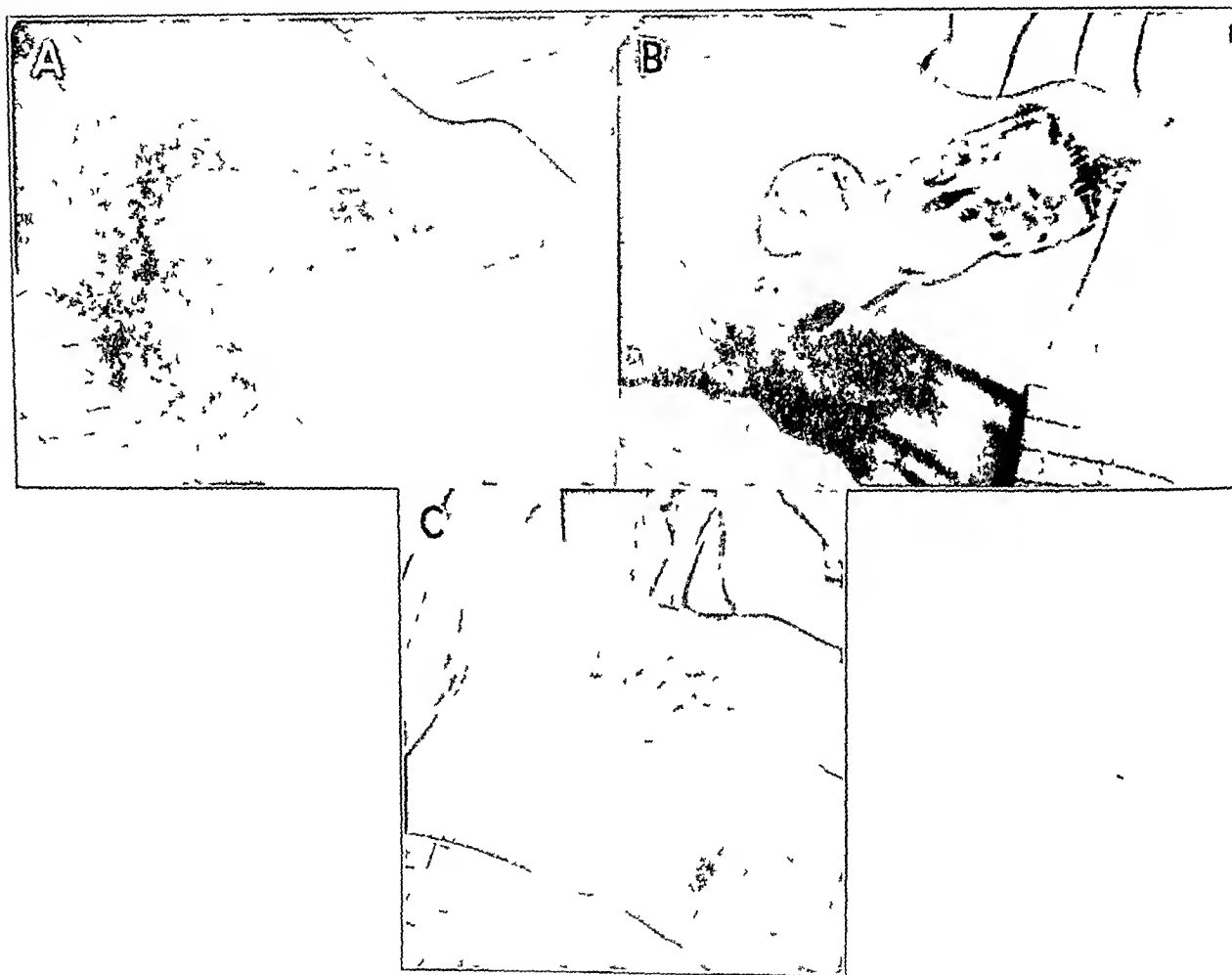


Fig 3—A, photograph of the ulcerated area eighty days after the operation and eight days after the last excision. Stubborn advance of necrosis continued at two points in spite of the last partial removal of the edge. Lighter patches through the upper half of the lesion now show clearly the extent of spontaneous growth of epithelium. The entire area is obviously smaller and the patient is free from symptoms. Another local excision was done. B, photograph of the lesion on the abdominal wall eighty-nine days after the operation and nine days after the last local excision. All activity at the margins has been eliminated, and the spread of the lighter area shows that nearly two thirds of the ulcerative bed has covered itself with new epithelium. At this time the use of sulfathiazole powder was discontinued and the growth of the remaining granulation tissue controlled by silver nitrate. C, photograph of the ulcerated area nearly completely healed, one hundred and nineteen days after the operation. Uncovered granulation tissue still shows in the suprapubic region and in a small spot above the crest of the ileum on the right side. The entire lesion has contracted to at least half its former width but gives the patient no disability. He is able to stand erect and has gained strength rapidly, with an actual increase in weight

spread of the ulceration. Sulfanilamide was unfortunately the only representative of the sulfonamide compounds that was tried locally before excision of the margins. Reliance was placed on this drug because of erroneous faith in the importance of a culture from the wound. However,

with a good blood supply which was later to become involved. To explain the failure of this treatment with these conclusions would imply that the gangrene resulted from bacterial action. This has not by any means been proved. The effect of higher concentrations of one of the

sulfonamide drugs should undoubtedly be determined. It is our opinion, however, that the victim of this type of ulceration deserves the more certain arrest of further expansion which surgical measures provide. Investigation in regard to the best way to accomplish this will be more fruitful than trials of medical treatment.

The first record of treatment of a lesion of this type by excision was presented in 1909 by Luckett, who stated that he made up his mind to treat his patient "wholly on surgical grounds and totally ablate the ulcer by actual cauterization." He added the remark that "the extent and magnitude of this procedure can be more fully grasped when we mention that we consumed the benzine of two freshly filled Paquelin thermocauteries in a period lasting fifty-five minutes." Cullen in his article that appeared in 1924, first attracted attention to this entity and gave an account of his final treatment with a "cautery knife used well beyond the advancing margin." Brewer and Meleney stated in 1926 that they were successful in their use of a deep barrier created by an encircling incision packed with frequent changes of gauze soaked in 0.4 per cent solution of formaldehyde. Shipley in 1928 published his account of successful excision with a red hot wire loop cautery to separate the margin from the healthy tissue and a knife to raise it from the underlying fascial layers. Lynn in 1931 advocated the use of the "cautery or electrotherm knife." Baker and Terry in 1932 used the Bovie electrosurgical unit and excised and coagulated the entire lesion. The ulceration in the case reported by Patterson in 1932 recurred after excision within the zone of redness and was later excised widely with the actual cautery. Holman in 1935 advocated excision with cautery and maggot therapy. Willard in 1936 apparently limited his technic of excision to the use of a knife. Scotson in 1933 used a trench cut out with "diathermy cautery" as a barrier, and James, another English surgeon, was successful with the same technic.

From this summary of the methods of excision it can be seen that the same surgical intention has been carried out by various appliances, which have tended to be more accurate, more hemostatic and less injurious to the surrounding tissues as electrical technics have been developed. These surgical methods have been sufficient, and their success has made the problem of causation of secondary importance, even though its solution might give the vague promise of a means of prophylaxis.

The statement from the article by Baker and Terry to the effect that they excised and coagulated the entire lesion may be referred to again

to emphasize a contrary opinion. One of the most fantastic features of our case was the spontaneous epithelization of the central area while the necrosis at the margins was still rapidly spreading. It was surprising that although the entire lesion grew to cover about two thirds of the surface of the abdomen, healing in the center had so far advanced at the time of the last excision that epithelization was complete in only twenty additional days. This rapid healing was obviously due to the miraculous appearance of islands of epithelium in places where the destructive necrosis had apparently been total. For this reason it is believed that coagulation of the entire lesion at any stage might have been a serious mistake.

REPORT OF A CASE

The appearance of this unexplained type of necrosis of a postoperative wound in a case in our service has been mentioned as a reason for this review of the subject. Certain details of this case have been mentioned in the discussion of the treatment, along with an enumeration of the standard measures that apparently failed. Effective treatment was not begun until the fifth-fourth day of the complication and it is freely admitted that at that time the condition was entirely out of control and the situation desperate. Limited excision of the active margins turned the tide, and the central areas proliferated healthy granulation tissue toward these margins. In the end, after three more partial excisions, we were convinced that less healthy tissue had been sacrificed than would have been with a massive excision. That the whole lesion seemed smaller rather than larger with each successive excision is well illustrated in photographs (figs 2 and 3).

SUMMARY

A review of articles presenting examples of progressive necrosis of postoperative wounds has been given, and from their tabulation the following observations have been made:

- 1 Progressive necrosis of postoperative wounds (sometimes termed phagedenic ulceration) is a clinical entity having a definite onset, characteristic features and a predictable course.

- 2 It occurs more frequently in males.

- 3 It develops most frequently in patients between the ages of 30 and 65 years.

- 4 This complication usually follows surgical procedures for drainage of septic conditions during the winter months.

- 5 It appears most frequently after removal of a gangrenous appendix and next frequently after costal resection for empyema.

6 All reports indicate that the only successful treatment is surgical excision of the affected area

From our observations made on the course and the treatment of this type of necrosis of post-operative wounds the following additional conclusions have been reached

1 A rapidly advancing necrotic margin involving skin and subcutaneous fat and following the spread of a dark red cutaneous inflammation which radiates from the operative incision is the characteristic picture of this condition. It is our feeling that spontaneous healing and rapid epithelization of the central portions of the ulcer are equally characteristic. The two processes proceed simultaneously, and there is no satisfactory evidence that any antiseptics so far applied have altered either process before the margins have been removed by excision. When this has been done, the spontaneous healing is so pronounced that a simple protective dressing is probably sufficient

2 Diagnosis may be made from the clinical picture and effective treatment instituted without confusing and controversial bacterial studies. The rare appearance of this condition reduces the importance of routine prophylaxis, and discussions should therefore stress the importance of early recognition and conservative excision

3 Early recognition of the characteristic changes in an operative wound and prompt adoption of treatment by excision will reduce this entity to a complication of relatively minor importance, with a short period of additional disability. Failure to adopt this surgical treatment promptly will result in weeks of uncertainty, a long period of disability and a disfiguring scar

4 Sulfathiazole given by mouth and sulfamidamide powder applied locally apparently have no effect on the progression of the gangrene before excision of the margins of the ulceration

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REGIONAL ENTERITIS

PATHOLOGIC STUDY OF TWENTY-TWO CASES

FREDERICK M OWENS JR, M D

CHICAGO

The condition known as "regional enteritis" was first established as an entity by Crohn, Ginzburg and Oppenheimer¹ in 1932. It has been variously referred to since that time as "terminal ileitis," "regional ileitis" and "regional enteritis." The last term is that most commonly accepted at the present time for the disease is not confined to the ileum but may involve any portion of the small bowel and even the large bowel.

Crohn and his collaborators emphasized the occurrence of different stages or phases of regional enteritis, which they characterized as (1) the acute inflammatory phase (2) the ulcerative phase, (3) the stenotic phase and (4) the phase of formation of fistulas. The first two might be referred to as acute stages and the last two as chronic. However, an important gross differential feature is the patchy or segmental involvement of the bowel. It should be emphasized that lesions of the different phases may be present in different segments and that all four types of lesions may coexist in the same bowel. Of course some of the features of regional enteritis are shared by other ulcerative diseases, especially by nonspecific ulcerative colitis. The latter differs, however, in its predilection for the colon, particularly for the descending portions of the colon. Grossly, there is relatively little similarity to specific infectious diseases which affect the intestines or to neoplastic diseases. Only occasionally a specific infectious disease, such as hyperplastic tuberculosis, resembles regional enteritis.

While little has been added to the excellent original description of the gross pathologic changes, descriptions of microscopic observations have usually been incomplete and variable. In part this may be accounted for by the small number of cases studied by any one observer.

Dr Eleanor Humphreys gave her assistance.
From the Department of Surgery of the University of Chicago.

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¹ Crohn, B B, Ginzburg, L, and Oppenheimer, G D. Regional Ileitis. A Pathologic and Clinical Entity, J A M A 99 1323 (Oct 15) 1932.

A careful review of microscopic material derived from 22 cases observed at the University of Chicago Clinics was undertaken. These cases provided examples of both acute and chronic stages of regional enteritis, as well as of major complications. This study has served to emphasize certain consistent microscopic features and to bring out certain differential criteria. For purposes of correlation and to avoid repetition, the microscopic observations in these cases have been summarized with particular reference to the changes occurring in the separate coats of the intestinal wall.

MATERIAL STUDIED

This survey is based on the study of multiple sections from various portions of each bowel or segment of bowel examined. The 22 cases represented a wide range in terms of acuteness or chronicity. The duration of symptoms was from eighteen weeks to thirteen years. There were 15 males and 7 females. The ages ranged from 12 years to 41 years, average 29.6 years. In 16 cases only surgically excised segments were available, but in 2 of these it was possible to examine sections of bowel removed at more than one operation. In 5 cases it was possible to compare observations on resected segments with those on remaining segments of the bowel obtained at autopsy. In 1 case only autopsy material was available.

MICROSCOPIC OBSERVATIONS

Changes in the Mucous Membranes—The earliest phase of inflammation has been, for obvious reasons, as yet unobserved. In early acute lesions (eighteen weeks) as well as in more acute lesions which coexisted with chronic ones, ulceration was already present. As established from gross observations, ulceration is usually patchy. The more acute ulcers tend to lie primarily on the mesenteric border, but with extension of the process they may encircle the lumen or may extend for considerable distances longitudinally. However, a characteristic feature, seen even where there is extensive ulceration, is the presence of islands of intact mucosa of varying size. In the less chronic stages such



Fig 1—Granulation tissue floor of a superficial ulcer, showing fragmented muscularis mucosae



Fig 2—Neuromuscular hyperplasia of the muscularis mucosae

islands often contain hypertrophied glands and project as pseudopolyps, overhanging the adjacent ulcers

The ulcers of the acute and subacute stages even when extensive, are often surprisingly superficial (fig 1). They frequently are confined to the mucosa, and when they do extend through the muscularis mucosae they rarely extend as far as the main muscular coats. In general, they have floors composed of an extremely

In the acute and subacute stages, the villi and the stroma between the glands are edematous and are densely infiltrated with inflammatory cells. Among these cells are some polymorphonuclear neutrophils and eosinophils, but the predominant cells are mononuclear cells.

In the more chronic stages the glands lose their hyperplastic features and eventually atrophy. Such glands are widely separated by a more fibrotic stroma, which still, however, may

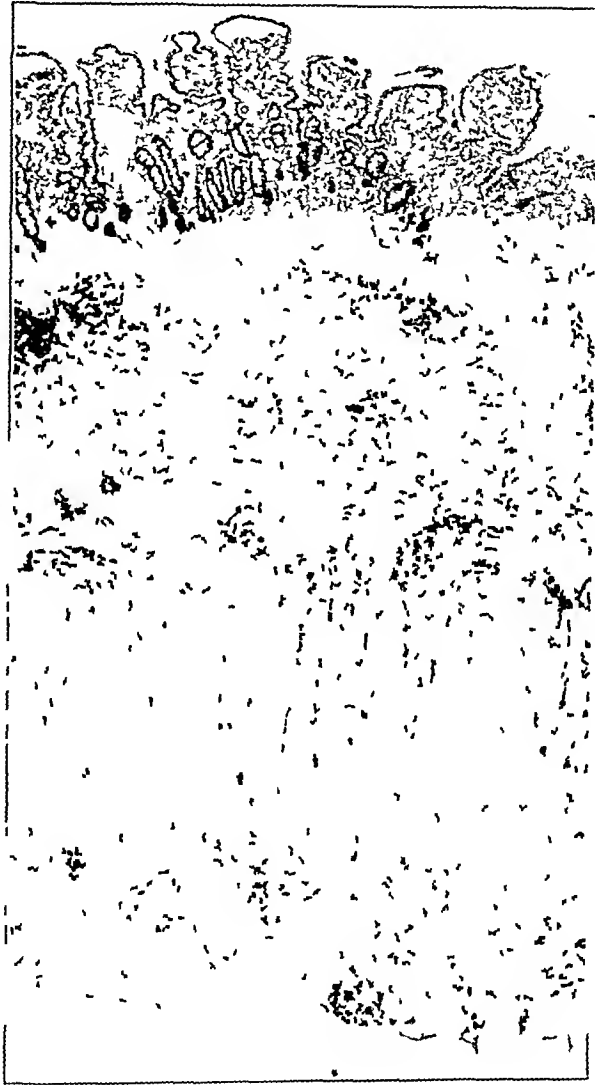


Fig 3—Section of the wall of the ileum, showing infiltration of the mucosa and submucosa by granulation tissue and fibrous tissue. Prominence of the ganglion cells of Auerbach's plexus is evident.

vascular granulation tissue, which contains, besides mononuclear cells of various types, moderate numbers of neutrophils and eosinophils and occasional giant cells. Not rarely thick layers of such granulation tissue lie on top of the muscularis mucosae. Productive fibroplasia in such superficial ulcers must be an important element, contributing to the subsequent stenosis. Deeper ulcers, which can be traced to sinus tracts, are not seen until the chronic stenosing phase is reached.

present evidence of some edema. The hypertrophic villi of the earlier stages tend also to disappear. In contrast to most intestinal lesions terminating in mucosal atrophy, however, the actual thickness of the mucous membrane is not decreased and may even be considerably increased. In fact, both the fibrosis and the edema tend to thicken it, another feature which contributes to stenosis.

The Muscularis Mucosae—Obviously this coat is destroyed by the deeper ulcerative lesions,

both acute and chronic. However, the extent of destruction is rarely great. A striking feature, evident fairly early and marked in the chronic phase, is proliferative thickening of this muscular coat. It is possible that this is of the nature of a neuromuscular hyperplasia, analogous to that seen in so-called "neurogenic" appendicitis. There is an increase in numbers of smooth muscle cells as well as a gross distortion of their normal pattern (fig 2). Such thick disarranged mus-

thick. Widely dilated small blood vessels are so numerous that it has the appearance of an unusually vascular granulation tissue. It is diffusely infiltrated by a cell-rich exudate, in which eosinophils abound. In more chronic stages much mature collagen is laid down. The diffuse exudate is replaced by a more focal reaction, with aggregates of mononuclear cells, which often resemble lymphatic follicles. Even in these stages some evidence of edema remains



Fig 4—Serosal tuberculoid granuloma containing giant cells

cular layers are seen both in the floors of superficial mucosal ulcers and beneath the islands of mucous membrane. They are not seen at any distance from the regions of major involvement. Single and grouped ganglion cells of Meissner's plexus may be found within or on either border of the distorted muscularis mucosae.

The Submucosa—The submucosal layer, in contrast to the outer coats, shares equally with the mucosa in the earliest stages that have been observed. It is extremely edematous and

The submucosal fibroplasia, perhaps even more than that in the mucosa, is a major cause of the thickening of the intestinal wall and the stenosis characterizing the chronic stages of regional enteritis (fig 3).

Muscular Coats—Exudative involvement of the heavy muscular coat is proportional to the activity in the two inner coats. In the earlier phases the most obvious change is the presence of mononuclear cells in focal deposits which seem to be associated with lymphatic channels. There

is only mild diffuse infiltration of the muscularis propria. The following features appear with chronicity. The muscular coats become thicker, their fibers are coarser and the neural elements in the wall are much more conspicuous. Groups of ganglion cells belonging to the plexus of Auerbach and their associated nerve fibers appear to be more abundant than in the uninvolved segments. It is possible that this is a relative increase, an increased prominence associated with contraction of the affected segment.

sclerosed and some appear to be occluded. The serosa is considerably thickened by edema and fibrosis, but increased prominence of blood vessels and of lymphatic channels likewise appears to play some part in this thickening. Of especial importance are the milium serosal nodules found in so many of these patients.² These gave early observers the impression that the disease was tuberculous in origin, although tubercle bacilli could not be isolated. These nodules are milium granulomas of nontuberculous origin con-



Fig 5—Giant cells lying in granulation tissue bordering a sinus tract

However, there are regions which strongly suggest that there is a true neuromuscular hyperplasia similar to that in the muscularis mucosae. These changes in the muscular and nervous elements are confined to the affected segments and are not found in the proximal (normal) segments or in the "skip areas," which lie between diseased segments. Even in the chronic stages there is comparatively little increase of connective tissue in the muscular layers.

Serosa—In the serosa the evidence of involvement of the lymphatics becomes more definite. About the lymphatic channels are aggregates of lymphoid cells, and many of the channels are

sisting of inflammatory round cells, epithelioid cells and giant cells (fig 4). Dispersed along the lymphatics of the serosa they form a middle link in the chain of lymphatic involvement so characteristic of this condition. This lymphatic involvement accounts for much of the edema, especially that of the later stages.

Mesentery and Lymph Nodes—Progressing along the lymphatics into the mesentery of the bowel are focal accumulations of inflammatory cells grouped here and there about lymphatic channels. In these lymphoid aggregations may

² Crohn, B. B. and Yumich, A. M. Ileocejunitis, *Ann Surg* 113: 371, 1941.

be found giant cells just as they are seen in the intestinal wall and the lymph nodes. The extent of involvement of the mesentery is largely dependent on the presence of sinus tracts. These sinus tracts which arise from mucosal ulcerations may penetrate the mesentery, where they are seen as spaces lined by granulation tissue which contains numerous giant cells (fig 5).

Pronounced lymphoid hyperplasia exists in the nodes draining the affected regions. This hyperplasia differs from simple hyperplasia in that one occasionally finds miliary tuberculoid granu-

les. In spite of determined efforts to isolate bacterial agents of disease from these specimens there have been no consistent findings. Tubercle bacilli were not found in guinea pigs which had been inoculated with specimens from 11 patients. In 5 cases colon bacilli were isolated from the intestinal wall and in 2 of these from adjacent lymph nodes. Of the remainder of the cultures that were made 5 were sterile and the rest yielded a heterogeneous collection of organisms. In view of the similarity of the two diseases it is significant that *Bacterium necrophorum*, which



Fig 6—Tubercle contained within a mesenteric lymph node

lomas containing giant cells within the nodes (fig 6). Isolated giant cells, many of which contain particles of apparent vegetable material, may be seen in the lymph nodes, as well as in the granulation tissue bordering the sinus tracts.

COMMENT

The uniformity of the microscopic characteristics observed in 22 cases of regional enteritis suggests a common causation for this entity. Although the etiologic agent has not been determined, this study suggests one or two possibilities.

Dragstedt, Dack and Kirsner³ were able to isolate from the diseased colon and also from the mesenteric lymph glands in a majority of cases of chronic ulcerative colitis, was not found in regional enteritis, although methods for its detection were rigorously applied.

Cutaneous tests with Frei antigen were done in 4 of the more recent cases, and all gave negative reactions. This result would tend to rule

3 Dragstedt, L. R., Dack, G. M., and Kirsner, J. B. Chronic Ulcerative Colitis. Summary of Evidence Implicating *Bacterium Necrophorum* as Etiologic Agent, *Ann Surg* 114: 653, 1941.

out the virus of lymphogranuloma venereum as the etiologic agent. Further examinations for parasites of pathogenic nature were consistently unsuccessful in 12 cases.

Although these results of bacteriologic examination in themselves are not striking, they are consistent with those obtained by other investigators who have been interested in this disease. There have been some reports from different regions of the isolation of similar strains of streptococci, but the glaring lack of any consistent ability to demonstrate these organisms on the part of many investigators is in itself significant. This search for an offending organism has been furthered by study of sections of this material treated with various types of special stains. The end result has been the inability to demonstrate any definite etiologic agent of organic nature.

The involvement of lymphatic channels suggests that an important cause of the changes in the intestinal wall may be the obstruction of lymphatic channels. This theory is supported by the observations of Reichert and Mathes,⁴ who reported in 1936 that they were able to produce changes similar to those of regional enteritis by chronic lymphatic obstruction. These changes were produced in dogs by the injection of

sclerosing agents into the lymphatics of the small intestine. It is possible that mesenteric lymphadenitis may in some way be a precursor of regional enteritis by setting up a chronic sclerosing reaction of the mesenteric lymphatics.⁵

However, the fact that pronounced neuromuscular hyperplasia is present in the involved portion of the bowel and is absent elsewhere may shed light on the causation of the disease. The factor of contraction must still be ruled out in accounting for the apparent increase of ganglion cells and the muscular hyperplasia. Further work must be done to determine with certainty the part played by longitudinal contraction of the bowel. But these neuromuscular changes appear to be proliferative rather than the effects of contraction. Whether there is a congenital abnormality of the innervation of the involved bowel to account for the neuromuscular changes cannot be said at the present time. The question of a localized allergic response as yet cannot be confirmed or denied and must be given fair consideration.

SUMMARY

A study of the microscopic features of 22 cases of regional enteritis revealed neuromuscular hyperplasia as a characteristic feature of the disease heretofore unreported. No conclusions can be reached as to the causation of the disease.

4 Reichert, F. L., and Mathes, M. E. Experimental Lymphedema of the Intestinal Tract and Its Relation to Regional Cicatrizing Enteritis, *Ann Surg* **104** 601, 1936.

5 Jackson, A. S. Regional Enteritis, *Surg, Gynec & Obst* **65** 1, 1937.

RESULTS OF LONG TERM EXPERIMENTAL CONSTRICTION OF THE HEPATIC VEINS IN DOGS

CHARLES D ARMSTRONG, MD, AND VICTOR RICHARDS, MD
SAN FRANCISCO

We have recently had the opportunity of observing a patient who presented at one time both polycythemia and thrombosis of the hepatic veins. This combination occurs not infrequently and has aroused the interest of clinicians for many years.¹ Most authors have assumed that thrombosis of the hepatic veins in this instance is secondary to thrombocytosis and slowing of the blood flow, but Oppenheimer^{1a} credited Weber with the suggestion that polycythemia may actually be the result of occlusion of the hepatic veins. We have been unable to trace this statement to the writings of Parkes Weber although he mentioned² "erythrocytosis due to stasis not of cardiac or pulmonary origin."

We hoped to resolve experimentally the order of appearance of polycythemia and thrombosis of the hepatic veins. To do this we produced occlusion of the hepatic veins by mechanical means and subsequently studied the effects on the blood.

From the Department of Medicine (Dr Armstrong) and the Department of Surgery (Dr Richards), Stanford University School of Medicine

1 (a) Oppenheimer, B S. Vascular Occlusion in Polycythemia Vera, *Tr A Am Physicians* **44** 338-344, 1929. (b) Baehr, G, and Klemperer, P. Thrombosis of the Portal and of the Hepatic Veins, *M Clin North America* **14** 391-410 (Sept) 1930. (c) Cole, N B. Comments on a Case of Polycythemia Rubra Vera with Autopsy, *ibid* **16** 1255-1266 (March) 1933. (d) Sohal, A R. Hepatic Complications in Polycythemia Vera with Particular Reference to Thrombosis of Hepatic and Portal Veins and Hepatic Cirrhosis, *Arch Int Med* **62** 925-945 (Dec) 1938. (e) Uhlhorn, E. Ueber Polycythämie mit Lebercirrhose, *Klin Wchnschr* **11** 2037-2038 (Dec 3) 1932. (f) Berk, L. Ueber Thrombose der Leberveinen nach umschriebener Thrombose im hepatischen Stück der unteren Hohlvene, *Beitr z path Anat u z allg Path* **90** 509-512, 1932. (g) McAlpin, K R, and Smith, K E. Polycythemia Vera. Report of Fourteen Cases Treated with Acetylphenylhydrozone, *New York State J Med* **38** 101-108 (Jan 15) 1938. (h) Altschule, M D, and White, G. Chiari's Syndrome in a Patient with Polycythemia Vera, *New England J Med* **220** 1030-1033 (June 22) 1939.

2 Weber, F P. Polycythemia, Erythrocytoses and Erythraemia (Vaquez-Osler Syndrome), London, H K Lewis Co, 1921.

OPERATIVE METHODS OF OCCLUSION OF THE HEPATIC VEINS

Winternitz³ ligated the hepatic veins in dogs and found no changes in the liver in a series of unfinished experiments. Other workers⁴ placed aluminum bands about the inferior vena cava above the hepatic veins and reduced the lumen of the veins by approximately 50 per cent. Necrosis of the liver and ascites ensued, the extent depending on the degree of constriction of the vena cava. The liver reverted to normal six days after the bands were removed.

An effective operation for temporary occlusion of the hepatic veins was described and used by Simonds and Brandes.⁵ Momentary occlusion of the veins caused a sudden drop in blood pressure and an abrupt return to normal. Longer constriction produced a fall in the concentration of hemoglobin and platelets in the blood, a decrease in blood sugar and blood calcium and an increase in coagulation time.⁶ After seven to thirty minutes of obstruction of the hepatic veins the hepatic cells became edematous and granular and there were hyperemia and dilatation of the sinusoids,⁷ which disappeared when the veins were released. Fibrosis of the central veins occurred after prolonged occlusion. It is stressed that the liver of the dog is resistant to anoxemia.⁸

3 Winternitz, M C. The Effect of Occlusion of the Various Hepatic Vessels upon the Liver, *Bull Johns Hopkins Hosp* **22** 396-404 (Nov) 1911.

4 Zimmerman, H M, and Hillsman, J A. Chronic Passive Congestion of the Liver, *Arch Path* **9** 1154-1163 (June) 1930.

5 Simonds, J P, and Brandes, W W. Effect of Obstruction of the Hepatic Veins upon the Systemic Circulation, *Am J Physiol* **72** 320-323 (April) 1925.

6 Brandes, W W. The Effect of the Mechanical Constriction of the Hepatic Veins, with Special Reference to the Coagulation of Blood, *Arch Int Med* **44** 676-692 (Nov) 1929.

7 Simonds, J P, and Callaway, J W. Anatomical Changes in Livers of Dogs Following Mechanical Constriction of the Hepatic Veins, *Am J Path* **8** 159-165 (March) 1932.

8 Simonds, J P, and Jergesen, F H. Late Changes in the Liver Induced by Mechanical Obstruction of the Hepatic Veins, *Arch Path* **20** 571-581 (Oct) 1935.

Using 9 adult dogs in good condition and under pentobarbital sodium anesthesia, we attempted to produce occlusion of the hepatic veins. The hepatic veins in the dog are numerous, thin walled, almost sinusoidal and quite inaccessible because of their posteromedial position over the dome of the liver. In each of our animals the occlusion was carried out through the abdominal cavity. We considered a transpleural-transdiaphragmatic route but have not actually used it.

Our initial technic followed the procedure described by Simonds and Brandes¹, certain details were later modified as the result of experience. The abdomen was opened by a transverse incision dividing both rectus muscles. An occlusive ligature was passed through the foramen of Winslow, forward over the left dome of the liver, around the anterior edge of the falciform ligament and backward over the right dome of the liver. To reduce the occluded tissue to a minimum the triangular ligaments were divided. The tie was made at the foramen of Winslow, and the ligature was left in place. Six of our 9 animals died, from hemorrhage caused by an inadvertent tear of the liver, from simultaneous occlusion of the inferior vena cava or from complete rapid occlusion of only the hepatic veins. Dog 1 died because of accidental ligation of the inferior vena cava together with ligation of the hepatic veins. Dog 2 was killed a week after the operation because of an infection in the eye, its liver was histologically normal. In dogs 4 and 5 the hepatic veins were acutely and completely occluded with steel wire ligatures. Each animal died within twelve hours of the operation, and sections of the livers showed central hyperemia of the hepatic lobules. Sudden complete occlusion of the hepatic veins seemed incompatible with life of the animal. In dogs 7 and 8 fenestrated rubber catheters were passed as ligatures and collodion was injected into the catheters. We hoped to occlude the veins by a ring of collodion which would subsequently shrink, but each dog died. Dog 7 died of hemorrhage from a tear of the liver, dog 8 died twelve hours after the operation, and autopsy disclosed rocklike collodion masses about the hepatic veins and other masses indenting the right renal vein. The right kidney was engorged, and the inferior vena cava was engorged but not occluded.

Dogs 3, 6 and 9 survived. Dog 3 had an artery tape passed around the hepatic veins and tied tightly enough to occlude them incompletely. Dog 6 had an artery tape tied loosely about the veins and soluble collodion injected along the tape with a needle. In dog 9 the hepatic veins

were incompletely occluded by a cellophane tape 5 mm wide tied as snugly as possible without being torn.

LABORATORY METHODS OF STUDY

Each of the 3 surviving dogs was carefully observed during the postoperative period and maintained on a constant, well balanced diet. Complete studies on the blood of each animal were done before the operation and at intervals thereafter. Blood was drawn by venipuncture of a jugular or a leg vein and placed in a tube containing a measured amount of anticoagulant. Packed cell volumes were measured in Wintrobe hematocrit tubes, spun for fifteen minutes at 3,500 revolutions per minute. Determinations of hemoglobin were done with a Sahli hemoglobinometer, in which 100 per cent equals 17 Gm of hemoglobin per hundred cubic centimeters. Plasma proteins were determined by the Kagan falling drop method. The electrophoretic fractionation

TABLE 1—Hemoglobin, Packed Cell Volume and Plasma Protein Values of Dog 3

Comment	Hemoglobin in %	Packed Cell Volume in %		Plasma Proteins in Gm / 100 Cc
		R B C	W B C	
3 days preop	110	52.5		6.7
1 hr preop	90	43		
1 hr postop	104			
18 hr postop, vomiting	110	52.5		6.7
2 days postop	88	33	1.0	6.7
3 days postop	90	41	1.8	6.2
8 days postop infection of the wound	92	48	1.8	6.2
13 days postop healing of the wound	86	44	1.1	6.0
27 days postop	99	49	1.1	
36 days postop	100	49	1.3	6.2
42 days postop	98	47	1.0	
50 days postop	96	47	2.0	6.9
63 days postop	90	45	1.2	6.4
73 days postop	98	46	1.2	
78 days postop	101	47.5	1.0	
83 days postop	110	47	1.5	7.1
102 days postop	110	48.3	1.1	6.8
114 days postop	100	48	1.3	6.8
128 days postop	100	47.1	1.8	6.5
147 days postop	95	48		
183 days postop	101	48	1.4	6.8
235 days postop serum taken for flocculation and electro- phoretic partition	84	47	1.2	6.8
245 days postop, laparotomy biopsy specimen of liver	76	43	2.3	7.8
246 days postop	84	38	0.9	8.2
270 days postop dog killed after laparotomy				

of the serum proteins was done by Dr Eloise Jameson according to Longsworth's modification⁹ of Tiselius' method.¹⁰ Cephalin-cholesterol flocculation tests¹¹ were done on the serum used for fractionation.

After each dog had survived the operation for more than six months, a second laparotomy was done in an effort to measure the pressure in the portal vein. The animals were then killed by thoracotomy, and the organs were removed from above downward with inclusion of the diaphragm. The ligature was identified with rela-

9 Longsworth, L. G. A Modification of the Schlieren Method for Use in Electrophoretic Analysis, *J. Am. Chem. Soc.* **61** 529 (Feb.) 1939.

10 Tiselius, A. Electrophoresis of Serum Globulin. II. Electrophoretic Analysis of Normal and Immune Sera, *Biochem. J.* **31** 1464-1477, (Sept.) 1937.

11 Hanger, F. M. Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin Cholesterol Emulsions, *J. Clin. Investigation* **18** 261-269 (May) 1939.

tion to the hepatic veins and the inferior vena cava before sections were taken for histologic examination

PROTOCOLS OF DOGS SURVIVING OPERATION

Dog 3—A male mongrel (artery tape loosely tied about the hepatic veins) had an uneventful postoperative course (table 1, fig 1) On the one hundred and ninety-

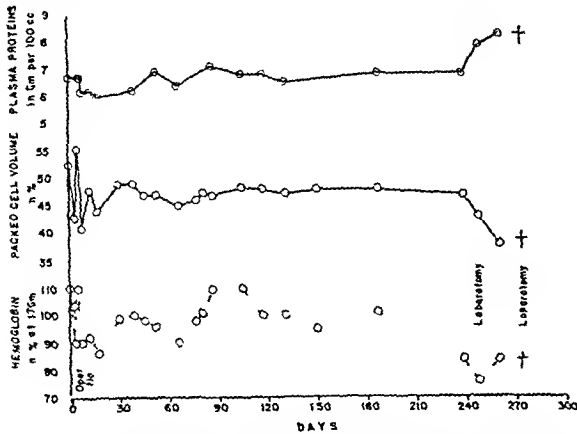


Fig 1—Changes in packed cell volume, hemoglobin and plasma proteins after obstruction of the hepatic veins of dog 3

seventh postoperative day an exploratory laparotomy was done. The liver was normal in size and appearance, and biopsy sections were normal. The ligature was easily isolated but was covered with small adhesions. The pressure in the portal vein was 13 cm of water. On the two hundred and thirty-second postoperative day laparotomy showed no change. The pressure in the portal vein was 9 cm of water. Postmortem examination revealed that the ligature surrounded the hepatic veins but that their ostia were widely patent. The liver weighed 360 Gm. The spleen was not enlarged. There was no evidence of collateral circulation. Sections

TABLE 2—Hemoglobin, Packed Cell Volume and Plasma Protein Values of Dog 6

Comment	Hemo globin in %	Packed Cell Volume in %		Plasma Proteins in Gm / 100 Cc
		RBC	WBC	
2 days preop	82	46		60
5 days postop, vomiting for 3 days postop	76	41	14	
13 days postop, condition fair	82	41	21	72
28 days postop, condition good	84	40	10	70
46 days postop, vomiting	83	41	10	
64 days postop, condition good, no ascites	81	40	10	
76 days postop	87	41	18	79
90 days postop	76	36.2	12	79
109 days postop, listless	76	36.5	13	79
145 days postop, melena	70	36	11	83
167 days postop, vomiting	81	33	31	
serum taken for flocculation test	68	31	17	73
207 days postop, ascites	56	29	11	88
215 days postop, listless ascites	56	30.1	19	88
223 days postop, dog killed after laparotomy	42	26.1	11	86
	64	31	22	60

of liver showed no histologic abnormality except in the region of the ligature, which was surrounded by a thin layer of fibrous tissue, macrophages and foreign giant cells. Sections of spleen, kidney and bone marrow were not remarkable.

Dog 6—A male bulldog (collodion-soaked artery tape tied about the hepatic veins) became progressively weaker after the third postoperative month, and ascites developed four months later (table 2, fig 2). On the two hundred and twenty-eighth postoperative day laparotomy revealed a huge liver adherent to the abdominal wall and the diaphragm. The pressure in the portal vein was 35 cm of water, that in the mesenteric vein, 16 cm of water. Postmortem examination showed only the hepatic veins encircled by the ligature, which was encased in a dense, hard collar of fibrous tissue. This fibrous collar narrowed the lumens of the veins 20 to 30 per cent and weighed 76 Gm. The liver weighed 1,040 Gm. The right lobe of the liver contained an encapsulated cyst 5 cm by 5 cm by 5 cm, filled with gelatinous yellowish material. No hooklets were found. The spleen was not enlarged.

Histologic sections showed a hepatic vein surrounded by a broad zone of loose fibrous tissue densely infiltrated by inflammatory cells, many of which lay in small abscess cavities. The cells were largely macrophages, polymorphonuclear leukocytes and plasma cells. A gram

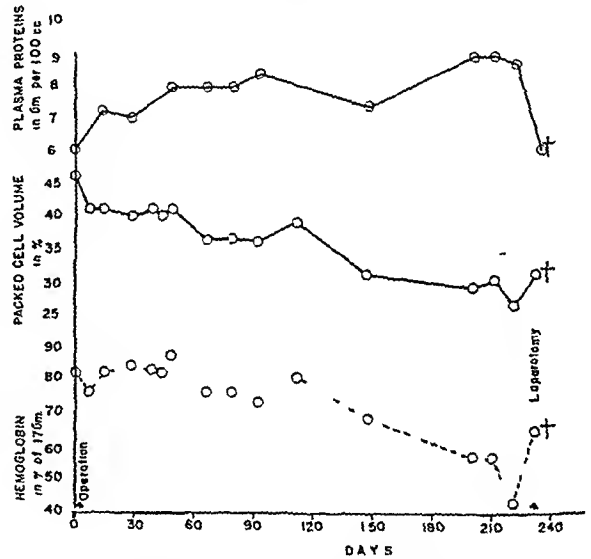


Fig 2—Changes in the packed cell volume, hemoglobin and plasma proteins after obstruction of the hepatic veins of dog 6

stain revealed no bacteria. Adjacent hepatic tissue contained similar inflammatory cells extending among the cells, and scattered small ducts through the zone of inflammatory reaction suggested that hepatic tissue had been destroyed. Elsewhere in the liver there was slight dilatation of the sinusoids, in some places so great as to cause complete disappearance of the hepatic cell cords between adjacent sinusoids. In one area the hepatic tissue had been replaced by a mass of large, loosely placed endothelium-lined spaces filled with blood. Everywhere the structure of the liver was distorted by perisinusoidal deposition of amyloid, which compressed the hepatic cell cords. Sections of kidney showed moderate deposits of amyloid in the glomeruli, the interlobular spaces and the walls of small arteries. The spleen contained large masses of amyloid scattered irregularly through the red pulp.

Dog 9—A female mongrel (cellophane tied about the hepatic veins) was in relatively poor condition at the time of operation but improved rapidly on a regular diet and ran a smooth postoperative course (table 3,

fig 3) Laparotomy on the one hundred and eighty-sixth postoperative day revealed a large, scarred liver. There was no ascites, and the pressure in the portal vein was not taken. Postmortem examination showed that the ligature enclosed only the hepatic veins and encroached 10 to 20 per cent on their lumens. The liver weighed 575 Gm, the spleen was not enlarged.

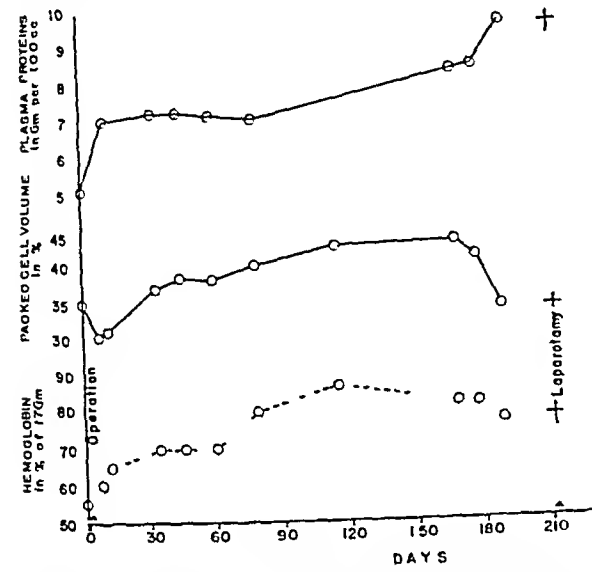


Fig 3—Changes in packed cell volume, hemoglobin and plasma proteins after obstruction of the hepatic veins of dog 9

Histologically the ligature was embedded in pus surrounded by a thick zone of cellular connective tissue resembling that found in dog 6. Near the capsule of the liver were localized areas of moderately dilated sinusoids and atrophied hepatic cells without obvious relation to the hepatic lobules. Near the hilus of the liver there was a moderate diffuse atrophy of the hepatic cells, and many Kupffer cells contained hemosiderin. Sections of spleen and kidney were not remarkable.

TABLE 3—Hemoglobin, Packed Cell Volume and Plasma Protein Values of Dog 9

Comment	Hemo globin in %	Packed Cell Volume in %		Plasma Proteins in Gm / 100 Cc
		R B C	W B C	
2 days preop, dog thin and in poor condition	55	35	10	51
5 days postop, condition good	60	30.5	13	70
10 days postop	65	31.1	11	72
22 days postop	70	37	11	72
45 days postop, vomiting, once	70	38.2	18	71
50 days postop, condition good	70	38	14	70
78 days postop	80	40		
114 days postop	87	42.5	11	
166 days postop, serum taken for flocculation test and electrophoretic protein fractionation	82	43	10	83
176 days postop, condition good	82	41	10	84
187 days postop	77	34	10	96
211 days postop, dog killed after laparotomy				

RESULTS

The initial blood values of each dog and of a control dog on a similar diet are gathered in table 4. Serum for protein fractionations and flocculation tests was obtained from dog 3 on the two hundred and thirty-fifth postoperative

day, from dog 6 on the one hundred and ninety-seventh and from dog 9 on the one hundred and sixty-sixth. Schlieren tracings of the electrophoretic patterns at two and one-half hours are reproduced in figure 4. The calculated protein fractions appear in table 5. Cephalin-cholesterol flocculation tests on the same serum yielded the results in table 5.

COMMENT ON RESULTS

The initial values of the packed cell volume of these dogs (table 4) have an average considerably higher than the 32.7 per cent reported by Kisch¹². The average initial values of the plasma proteins are also somewhat higher than the aver-

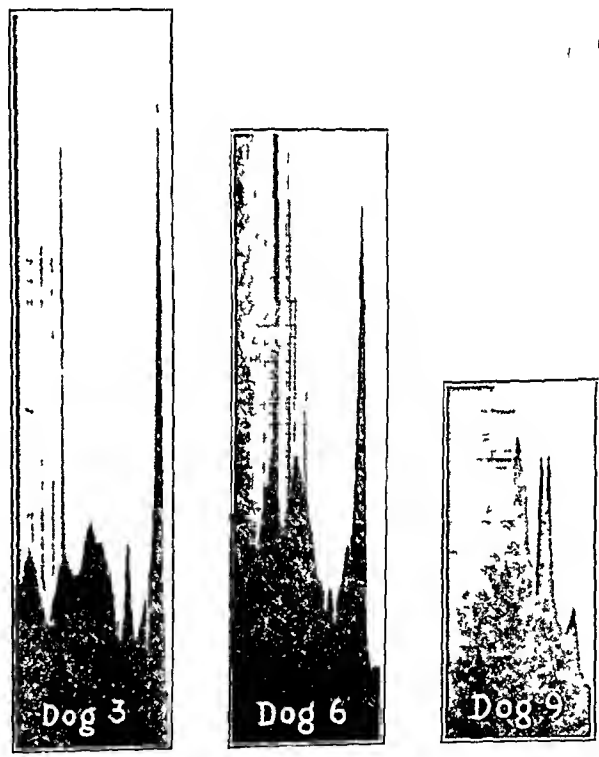


Fig 4—Schlieren tracings at two and one-half hours, showing results of electrophoretic protein fractionation in dogs surviving obstruction of the hepatic veins

ages of 4.9 Gm per hundred cubic centimeters¹³ and 6.2 Gm per hundred cubic centimeters¹⁴ found in other series. The packed cell volumes, red cell counts, hemoglobin values and plasma protein levels were higher in the male dog than in the female. Administration of pentobarbital

12 Kisch, B., and Strauss, E. Hematocrit Readings of Normal Dogs, *Exper Med & Surg* 1:250-251 (Aug) 1943.

13 Elman, R. Acute Hypoproteinemia Following a Single Severe Hemorrhage in the Fasting Dog, *Am J Physiol* 128:332-337 (Jan) 1940.

14 Achard, C., Bariety, M., Codouris, A., and Hadjigeorges, E. Amylose experimentale et perturbation de l'équilibre protidique du sang chez le chien par injections intraveineuses de caseinate de soude. *Compt rend Soc de biol* 108:702-704, 1931.

sodium produced in most instances an effect suggestive of hemodilution

Polycythemia developed in none of the 3 dogs which survived attempts to ligate the hepatic veins. Although in each animal the procedure was different and a different degree of occlusion of the hepatic veins was thereby produced, these results support the popular view that polycythemia precedes thrombosis of the hepatic veins when the two conditions coexist.

Anemia and hyperproteinemia did develop in each of the surviving animals. These changes

albuminuria of renal amyloidosis. Protein fractionation showed extreme hypoalbuminemia and hyperglobulinemia by virtue of increases in alpha and beta globulin, changes, in a word, similar to those reported by Longworth and associates¹⁵ in cases of obstructive jaundice. Hyperglobulinemia has been reported in experimental animals¹⁶ and in human beings¹⁷ with amyloidosis, but it has not been made clear whether hyperglobulinemia is primary or secondary to the deposit of amyloid. The instance reported here sheds no light on this problem. Leutscher's^{17a}

TABLE 4—Initial Blood Values of All Experimental Dogs with Reference to Sex and Weight, Comparison of Values Before and After Anesthesia Induced with Pentobarbital Sodium

Animal	Sex	Weight, Kg	Comment	RBC*	WBC†	Hemo globin per Cent	Packed Cell Volume, per Cent	Plasma Protein‡
Dog 1	M		Before operation	4.9	10,175	82	42	
			After operation	5.1	8,700	82		
Dog 2	M		Before operation	5.6	8,550	84		
			After operation	5.4	5,400	72	33	
Dog 3	M		Before operation	6.0	15,300	110	52.5	6.7
			After operation	5.4	12,350	90	47	
Dog 4	F	12.0	Before operation				30	4.6
Dog 5	M	10.0	Before operation	6.3		100	50	6.1
Dog 6	M	12.6	Before operation	6.4		82	46	6.0
Dog 7	M	15.0	Before operation	7.4		105	49	6.3
Dog 8	M	10.0	Before operation	6.5		100	48	6.7
Dog 9	F	11.3	Before operation	4.6		55	35	5.2
Control	M		No operation			106	51.2	6.9
				Male and Female		Male	Female	
Average packed cell volume (10 dogs)				47.6		46.4		32.5
Average initial red blood cells (10 dogs, 9 male, 1 female)				6.1		6.2		
Average initial hemoglobin in per cent (9 dogs, 8 male, 1 female)				91.4		96.1		
Initial plasma proteins (5 dogs, 6 male, 2 female)				6.0		6.4		4.8

* RBC = millions of red blood cells per cu mm of blood

† WBC = white blood cells per cu mm of blood

‡ Plasma proteins are expressed in Gm per hundred cubic centimeters of blood

TABLE 5—The Results of Cephalin-Cholesterol Flocculation Tests and Electrophoretic Fractionation of Proteins in Dogs Surviving Occlusion of the Hepatic Veins

Dog	Post operative Day	Cephalin-Cholesterol Flocculation		Total Protein (Kagan) Gm / 100 Ce	Electrophoretic Fractionation (Calculated from Schlieren Diagram at 2½ Hr)									
		24 Hr	48 Hr		Albu min in %	Albu min in Gm	α ₁ in %	Glob ulin in Gm	α ₂ in %	Glob ulin in Gm	β ₁ in %	Glob ulin in Gm	β ₂ in %	Glob ulin in Gm
3	230	0	0	65	26.1	1.77	10.6	0.72			19.8	1.30	19.0	1.29
6	197	---	+++	85	10.1	0.88	15.6	1.37	13.4	1.18	33.6	2.96	18.5	1.63
9	160	0	±	83	2.07	2.66	6.03	0.60	3.42	0.28	31.96	2.65		

appeared after seven months in the dog with a minimum of occlusion of the hepatic veins and hepatic damage (dog 3). Electrophoretic fractionation of the proteins in this dog showed some hypoalbuminemia at a time when the total protein level was at the upper limit of normal. Progressive anemia and hyperproteinemia appeared in dog 6 one month after operation, but the interpretation of these changes is difficult because of the simultaneous and probably tortuous development of amyloidosis in this animal. The terminal decline in total protein of the blood in this dog was probably due to the

15 Longworth, L. G., Shedlovsky, T., and MacInnes, D. A. Electrophoretic Patterns of Normal and Pathological Human Blood Serum and Plasma, *J. Exper. Med.* **70**: 399-413 (Oct.) 1939.

16 Achard et al.¹⁴ Longworth et al.¹⁵

17 (a) Eklund, C. M., and Reimann, H. A. The Etiology of Amyloid Disease, *Arch. Path.* **21**: 1-9 (Jan.) 1936. (b) Tiber, A. M., Pearlman, A. W., and Cohen, S. E. Hepatic Function in Patients with Amyloidosis, *Arch. Int. Med.* **68**: 309-324 (Aug.) 1941. (c) Pearlman, A. W. Amyloidosis: A Clinical and Pathological Study of One Hundred and Thirty-Five Cases, *Quart. Bull. Sea View Hosp.* **6**: 295-308 (April) 1941. (d) Leutscher, J. A. Electrophoretic Analysis of Plasma and Urinary Proteins, *J. Clin. Investigation* **19**: 313-320 (March) 1940.

electrophoretic separations showed an increase in gamma globulin in a patient with amyloidosis.

Anemia and hyperproteinemia developed in dog 9 three to four months after operation. Here the electrophoretic pattern showed a moderate hypoalbuminemia and the hyperglobulinemia was due to an increase in the beta and gamma globulin fractions. In dogs 6 and 9 a rise in plasma protein and a fall in packed cell volume foreshadowed future changes as early as the first postoperative week.

Kabat and co-workers¹⁸ found that flocculation of cephalin-cholesterol mixtures depended on an increase in serum gamma globulin. In these animals flocculation was obtained only with serum in which the gamma globulins were relatively and absolutely reduced in amount. It was once widely accepted that cirrhosis or other forms of hepatic damage led to a diminution of serum protein. Recent writers have stressed the frequency of hyperglobulinemia in diseases of the liver.¹⁹ Usually there is enough concomitant

hypoalbuminemia so that the total protein level remains normal but distinct increases in total protein may occur.²⁰ Hypoalbuminemia and hyperglobulinemia in the presence of damage to the liver suggest a principally hepatic source of serum albumin and a multiple origin of serum globulin.²¹ Globulin may be formed in part in the cells of the reticuloendothelial system.²²

Anemia and hyperproteinemia have not been reported in the obstruction of human hepatic veins, thus the human counterpart of this experimental syndrome is not available. It is probable, however, that hyperglobulinemia occurs in hepatic damage resulting from occlusion of the hepatic veins in human beings, and anemia is common with other forms of disease of the liver resulting in cirrhosis. Whipple has demonstrated a 40 per cent diminution of hemoglobin production factors with the hypoproteinemia (i.e., hypoalbuminemia) of cirrhosis.²³

SUMMARY

Ligation of the hepatic veins was attempted in 9 dogs. Three survived the operation for two hundred and eleven, two hundred and twenty-eight and two hundred and seventy days. In each of these dogs anemia and hyperproteinemia developed. Hypoalbuminemia and hyperglobulinemia were demonstrated by electrophoretic fractionation of protein. The gross and histologic observations on each animal are described. Amyloidosis, probably unrelated to ligation of the hepatic veins, developed in 1 animal. These experiments suggest that polycythemia precedes thrombosis of the hepatic veins when the two diseases occur concomitantly. The concept of extrahepatic formation of serum globulin is supported.

20 Amberg, S. Hyperproteinemia with Severe Liver Damage, Proc Staff Meet, Mayo Clin **17** 360-362 (June 10) 1942. Cardon and Atlas^{19h}

21 Loeb^{19a} Madden and Whipple^{19f}

22 Loeb^{19a} Bing^{19e}

23 Whipple, G. H., and Robscheit-Robbins, F. S. Hemoglobin Production Factors in Human Liver Anemias, Hypoproteinemia, Cirrhosis, Pigment Abnormalities and Pregnancy, J Exper Med **76** 283-298 (Sept) 1942.

18 Kabat, K. A., Hanger, F. M., Moore, D. H., and Andrews, H. Relation of Cephalin Flocculation and Colloidal Gold Reactions to Serum Proteins, J Clin Investigation **22** 563-568 (July) 1943.

19 (a) Loeb, R. F. Plasma Proteins in Health and Disease, New England J Med **224** 980-987 (June 5) 1941.

(b) Janeway, C. A. The Plasma Proteins, Their Importance in Clinical Medicine and Surgery, ibid **229** 751-756 (Nov 11), 779-785 (Nov 18) 1943.

(c) Kagan, B. M. Studies on the Clinical Significance of the Serum Proteins, Arch Int Med **71** 157-163 (Feb) 1943.

(d) Jeghers, H., and Selesnick, S. Hyperproteinemia: Its Significance, Internat Clin **3** 279 (Sept) 1937.

(e) Bing, J. Further Investigations on Hyperglobulinemia, Acta med Scandinav **63** 547-564 and 565-583, 1940.

(f) Madden, S. C., and Whipple, G. H. Plasma Proteins: Their Source, Production and Utilization, Physiol Rev **20** 194-217 (April) 1940.

(g) Casten, D., Bodenheimer, M., and Archam, I. A Study of Plasma Protein Variations in Surgical Patients, Ann Surg **117** 52-73 (Jan) 1943.

(h) Cardon, L., and Atlas, D. H. Incidence and Causes of Hyperproteinemia, Arch Int Med **71** 37-390 (March) 1943.

(i) Post, J., and Patek, A. Serum Proteins in Cirrhosis of the Liver: Relation to Prognosis and to Formation of Ascites, ibid **69** 67-72 (Jan) 1942.

(j) Nitrogen Balance Studies on Five Patients, ibid **69** 83-89 (Jan) 1942.

(k) Serum Proteins in Relation to Liver Disorders, Bull New York Acad Med **19** 815-830 (Dec) 1943.

CHEMOSURGICAL TREATMENT OF CANCER OF THE LIP

A MICROSCOPICALLY CONTROLLED METHOD OF EXCISION

FREDERIC E MOHS, M D

MADISON, WIS

In the treatment of cancer of the lip a chemosurgical procedure offers certain important advantages. As previously described,¹ the chemosurgical method was devised to provide a microscopically controlled means for the excision of various accessible forms of cancer. The method entails, first, chemical fixation of the suspected tissues in situ and, second, systematic excision and microscopic examination of the fixed tissues. This process of fixation, excision and microscopic examination is repeated until a microscopically cancer-free surface is reached. The main advantages conferred by the microscopic control are (1) unprecedented reliability and (2) conservatism.

tolytic, such as dichloroacetic acid or a saturated solution of trichloroacetic acid, is applied until the surface becomes white. Keratolysis is necessary to render the keratin layer permeable to zinc chloride. If the keratin layer is hard and thick, it may be necessary to scrape the surface repeatedly and reapply the keratolytic.

The zinc chloride fixative is then applied to the cancer in a thickness varying from less than 1 mm to 3 mm or more, depending on the depth of penetration required. When the cancer is large the dose is at first correspondingly large, but as a cancer-free level is approached the dose is reduced. The formula of the fixative paste now used in our clinic is as follows:² 40 Gm of stib-



Fig 1—Example of dressing used for a large cancer of the lip

TECHNIC

Preparatory to the first application of the fixative the skin surrounding the cancer of the lip is freshly shaved, all crusts and scales are removed from the surface of the tumor and a kera-

mite (80 mesh sieve), 10 Gm of powdered sanguinaria and 34.5 cc of a saturated solution of zinc chloride.

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From the Department of Surgery, Dr. E. R. Schmidt, Chief, State of Wisconsin General Hospital and the McArdle Memorial Laboratory for Cancer Research.

1 (a) Mohs, F. E., and Guver, M. F. Pre-Excisional Fixation of Tissues in the Treatment of Cancer in Rats, *Cancer Research* 1:49 (Jan) 1941. (b) Mohs, F. E. Chemosurgery. A Microscopically Controlled Method of Cancer Excision, *Arch Surg* 42:279 (Feb) 1941.

The applied fixative is then covered with cotton, and this in turn is covered with an overlapping gauze-covered cotton dressing on which petrolatum has been spread to make it air tight. The dressing is then securely affixed with strips of quarter-inch or half-inch adhesive tape applied transversely and following the contour of the tumor (fig 1). If the lesion extends back into

2 As previously pointed out,^{1a} various other materials may be substituted for stibnite and for sanguinaria. The most satisfactory substitute for stibnite is made from clinkers from bituminous coal by grinding and passing them through an 80 mesh sieve. Rye flour is a satisfactory substitute for powdered sanguinaria.

the oral mucosa it is often desirable to place half-inch or 1 inch (1.25 or 2.5 cm) tapes over the dressing in an anterior-posterior direction, extending from the skin of the chin externally to the gingivolabial sulcus internally. The tape in the latter position is held in place by the pressure between the teeth and the lip, though of course it does not adhere to the oral mucosa.

Dressings at the corner of the mouth are similar to those of the lower lip except that the half-inch tapes from the upper and lower lips and from the cheek converge on the mucosal side, where they are held in place by pressure between the cheek and the teeth. Dressings for the upper lip are similar to those of the lower lip.

The patient is then instructed to drink his liquids through a straw or a glass tube and to use care while eating to avoid undue soiling and movement of the dressing. Analgesics, vary-

After the first layer of tissue is excised it is usually possible to differentiate the fixed cancerous tissue, with its dead white color and crumbly consistency, from the fixed normal tissue, with its gray color and firm consistency. When cancer is thus grossly visualized, sections of the entire plane are unnecessary and only specimens for pathologic diagnosis are taken. If, however, the cancer is small, it is sometimes feasible to cut a section horizontally through the under surface of the first-removed specimen, and if this plane is free of cancer no further treatment is necessary.

When more cancerous tissue is known to be present the zinc chloride fixative is reapplied to the surface exposed by the first excision. Again the dose is judged to give the desired penetration. Twenty-four hours later another layer of tissue is excised (fig 2A, second incision). If as

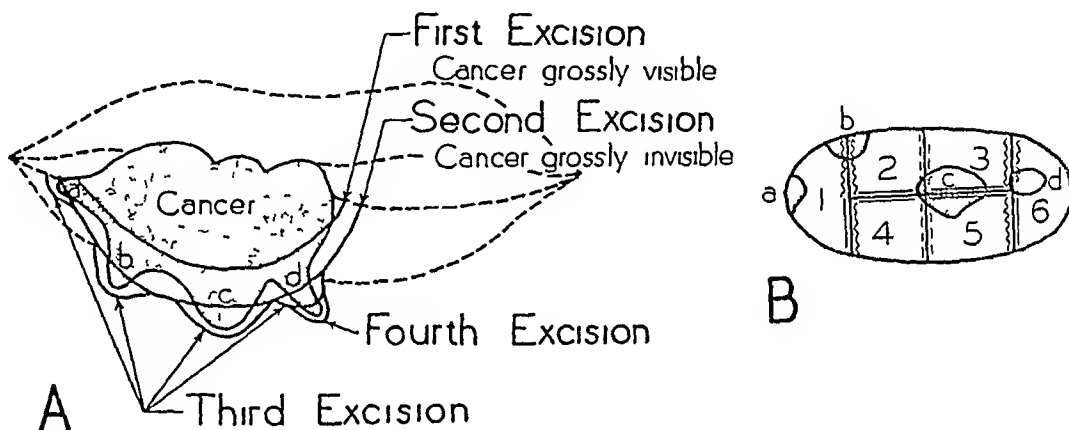


Fig 2—Diagram illustrating the chemosurgical technique. A (front view), cancer of the lower lip, indicated by stippled area, with outgrowths *a*, *b*, *c* and *d*. After daily chemical fixation of the tissues in situ, excisions are carried out at the four levels indicated. After the first excision the cancer (in this example) is grossly visible but after the second excision the cancerous tissue cannot be recognized grossly. Therefore, the second excised layer is divided into specimens and mapped as shown in B (top view). Frozen sections cut through the under surface of the specimens reveal cancer in areas *a*, *b*, *c* and *d*, corresponding to the downgrowths in A. Only the cancerous areas are again fixed and excised, and the process is repeated until a cancer-free plane is reached.

ing from acetylsalicylic acid to codeine or even morphine, may be prescribed according to the extent of the lesion and the sensitivity to pain of the patient, often no analgesic is required. The patient usually remains ambulatory, often going about his business as usual.

After twenty-four hours the first layer of fixed tissue is excised with a scalpel (fig 2A, first excision). Since the incision is made through killed and fixed tissue, there is no pain or bleeding from this operation unless the incision is inadvertently carried too deeply. If bleeders are encountered they are controlled by applying a small square of gauze impregnated with the fixative under momentary pressure. Bleeding from the labial and the external maxillary artery can readily be stopped by this means.

In the diagrammed example, the extensions of cancer at this level are small in caliber, they are invisible to the naked eye and their detection requires microscopic examination of the under surface of the excised layer.

This microscopic examination is accomplished by dividing the layer into specimens as it is removed. The edges of the specimens are marked with India ink, blue ink and mercurochrome for orientation (indicated by wavy broken and solid lines respectively on the map in figure 2B), and a map of each specimen is drawn on the lesion (with mercurochrome or ink) and on a pad of paper (fig 2B). The lesion is covered temporarily with moist cotton to prevent hardening of the surface while the frozen sections are being made and examined.

The specimens, having been fixed in situ, are usually firm and form retaining, and they are immediately cut through their under surfaces with a freezing microtome. The sections are stained with hematoxylin and eosin, cleared and mounted in clarite. The resulting sections, which have satisfactory microscopic detail for ready diagnosis (fig 3), are immediately examined and the areas of cancer recorded on the map in red pencil. (Cancerous areas are stippled in figure 2 B). The india ink blue ink and mercurochrome markings for orientation are readily visualized at the edges of the sections.

After the exact location of the remaining cancer has been determined the fixative is reapplied only to the cancerous areas. Twenty-four

and relatively slight deformities are obtained.

In advanced stages in which sufficient lip structure is removed to require a plastic repair, the tissues, because of their good vascular supply, lend themselves well to surgical procedures. Moreover, the preservation of a maximum amount of uninvolved tissue gives the surgeon more tissue with which to accomplish a favorable cosmetic result without the use of grafts.

THERAPEUTIC RESULTS IN CASES OF CANCER OF THE LOWER LIP

At the time of writing a total of 197 microscopically proved squamous cell carcinomas of the lower lip have been treated chemosurgically. However, a minimum of six months must elapse



Fig 3—Photomicrograph of a squamous cell carcinoma of the lower lip which had been fixed in situ with zinc chloride. There was some shrinkage of cells, but the histologic diagnosis was readily made.

hours later another layer is excised from each of the treated areas (fig 2 A, third excision), and the tissues still containing cancer are again treated and excised (fig 2 A, fourth excision).

When a plane completely free of cancerous tissue is reached (e.g. fig 5 B), the wound is covered with a gauze or cotton dressing spread with petrolatum to prevent excessive drying and shrinkage of the remaining thin layer of fixed tissue. Three days later this final layer of fixed tissue may be removed by snipping the holding strands of fibrous tissue with scissors (fig 5 C). If desired, it may be left another day or so to separate spontaneously.

The resulting smooth, highly vascular, germ-resistant granulation tissue supports the exceptionally rapid growth of the epithelium across the wound. During healing it is optional either to apply a gauze dressing spread with petrolatum or simply to apply petrolatum directly to the undressed wound. As a result of the favorable conditions for healing, exceptionally comely scars

before any significance can be attached to the results. Accordingly, material in the following sections (up to the section on three year and five year results) concerns the cases of 176 consecutive patients admitted to the chemosurgery clinic between July 7, 1936 and May 29, 1943, the latter date being more than six months previous to the time of writing.

The lesions of these patients were in all stages. All but 4 of the 176 patients were men. The patients ranged from 22 to 91 years of age, with an average age of 62.6 years.

Primary Lesion—Of the 176 squamous cell carcinomas of the lower lip treated chemosurgically, 172 primary lesions were completely eradicated (97.7 per cent) as far as can be determined at the time of writing by a careful follow-up for a period of from six months to over seven years. Chemosurgical treatment of 4 lesions was unsuccessful. Three were incompletely treated because when it became apparent that the cancer had invaded the entire body of

the mandible as well as the entire lip and chin, therapy was stopped at an optimal palliative level. The unsuccessful treatment of the fourth was due to the poor cooperation of a demented patient, who persistently removed the dressing from his advanced cancer, a surgical excision was therefore done, also without success. There were no failures that could be attributed to a fault in the method.

All but 2 of the 172 primary lesions were eradicated by the first series of treatments. Both of these were deep-seated carcinomas, recurrent after radium and roentgen therapy, in which outlying masses, disconnected from the original tumor, were present. These disconnected masses are occasionally found after part of a tumor has been killed by irradiation, and they constitute

therapy for inoperable nodes, while 2 patients refused any treatment for their nodes.

Of the 16 metastatic lesions in patients with controlled primary lesions only 5 became apparent after removal of the cancer of the lip. Thus, of 176 cases of this series in only 5 (2.8 per cent) was there involvement of nodes which made its clinical appearance after the chemosurgical treatment. This low incidence of metastasis confirms our previous findings that chemosurgical treatment has no tendency to increase metastasis in rats^{1a} or in human beings^{1b}.

In regard to the treatment of metastatic nodes, my present practice is to refer for surgical neck dissection all patients having freely movable metastatic nodes. Patients with nonpalpable nodes or with small, shotty, benign-feeling nodes are



Fig 4—Example of primary lesion of group A (average diameter, under 1 cm). A, squamous cell carcinoma in a young woman, B, granulations after removal of final layer of fixed tissue, C, healed lesion. The patient is free of cancer after four years.

a hazard calling for more than usual care in check-ups following chemosurgical treatment. At any rate, these 2 carcinomas also finally responded successfully to subsequent chemosurgical treatment.

Regional Metastasis—Metastasis to the regional lymph nodes occurred in 20 patients. Four of these were the previously mentioned patients with incompletely treated primary lesions, while the remaining 16 had no evidence of residual cancer at the primary site. Of these 16 patients, 6 had successful surgical dissections of the nodes by Dr. E. R. Schmidt and his staff, in 1 the nodes recurred after several chemosurgical and surgical dissections, 2 had partial chemosurgical dissections, but the nodes were found to be too extensive for complete removal, 1 had an unsuccessful surgical dissection two years later in another city, 4 received palliative roentgen

not subjected to prophylactic neck dissections unless the primary lesion is large and/or the microscopic grade of malignancy is high. When large, metastatic submental or submaxillary nodes are fixed to the mandible but there are yet no inoperable metastatic lesions evident in the cervical chain, I at times remove the mass chemosurgically as will be described later in this paper. Patients with hopelessly extensive metastatic nodes are usually referred for palliative roentgen therapy.

End Results After Six Months or More—While end results after six months are of limited use for the comparison of the chemosurgical method with other methods they come within a very few per cent of indicating the true ultimate prognosis in regard to the cancer. The latter statement is true because residual foci of cancer, if left after chemosurgical treatment make them-

selves apparent well within six months, they are not trapped deep in a surgical scar or in an atrophic radiation scar where they cannot be detected at an early date. Moreover, as mentioned previously, metastatic nodes rarely appear after chemosurgical removal of the primary lesion, and if they do they almost always appear within six months.

The 176 cases are divided into "indeterminate" and "determinate" groups. The indeterminate

check-up visits but who was reported to have a submaxillary mass later, treatment was counted as a failure.

For the 168 cases of the determinate group the cure rate after six months or more was 91.7 per cent (table 1).

Effect of Size of Primary Lesion on Prognosis—In the 168 cases in the determinate group the primary lesions were divided into four groups according to their average diameter. A, under

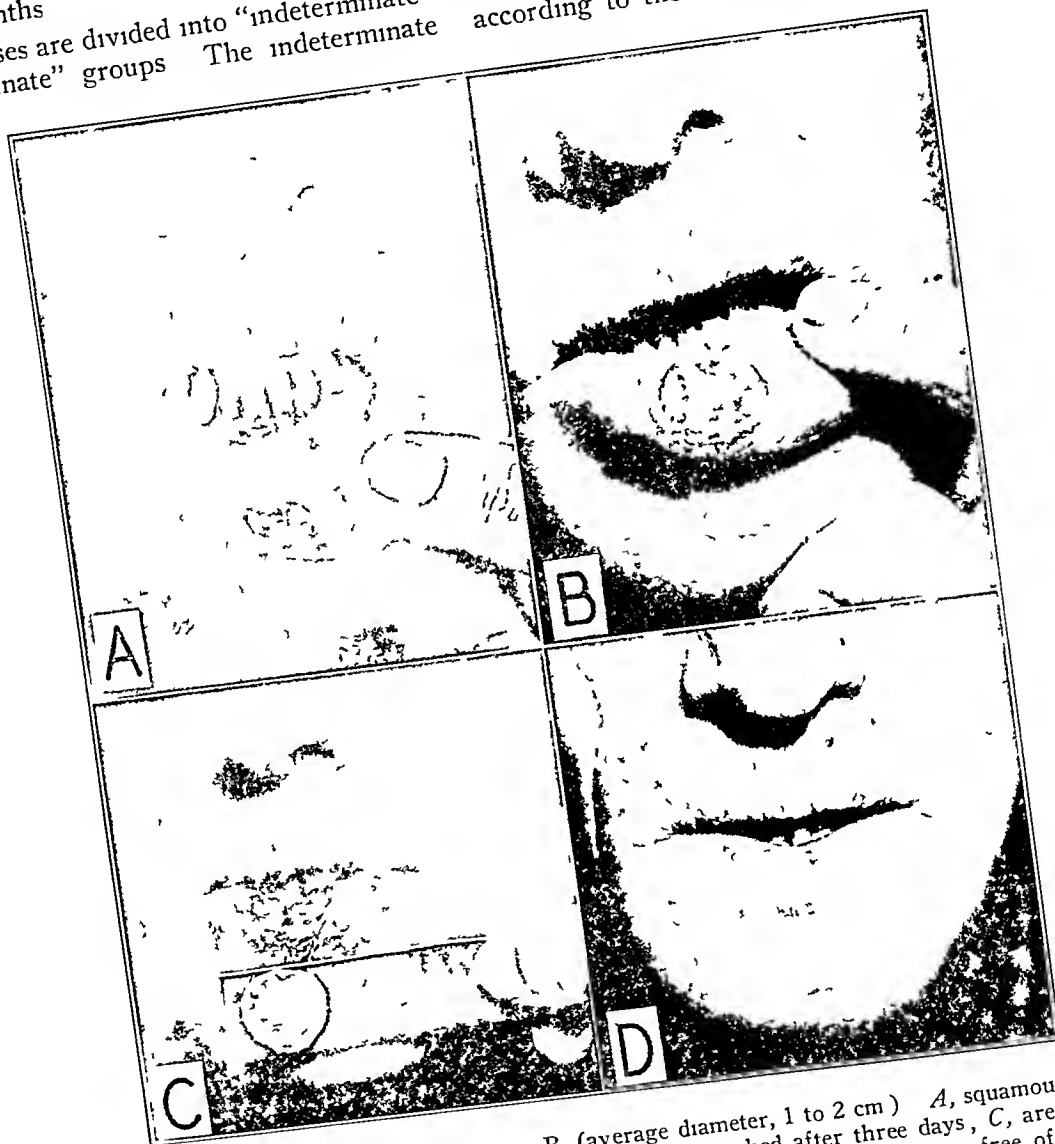


Fig 5—Example of primary lesion of group B (average diameter, 1 to 2 cm). A, squamous cell carcinoma, B, area of fixed tissue at the microscopically cancer-free plane reached after three days, C, area of granulations and removed layer of fixed tissue four days later, D, healed lesion. The patient remains free of cancer after five years.

group includes those cases in which patients have died of intercurrent diseases without evidence of cancer and in which they have been lost from observation without cancer. The determinate group includes those cases in which patients have died of cancer, have been lost from observation with cancer, or are living with cancer and those cases in which patients have been free of cancer for six months or more. For 1 patient who seemed well at his six and nine month

1 cm (fig 4), B, 1 to 2 cm (fig 5), C, 2 to 3 cm (figs 6 and 8), and D, 3 cm or more (fig 7). The average size of all the cancers was 1.74 cm.

The end results in the four groups after six months or more indicate a striking correlation between the extent of the primary lesion and the prognosis (table 2). The less favorable results with increasing size are mainly due to the greater incidence of metastasis of the larger lesions,

but it is also of interest to note that the 4 primary lesions which were not eradicated were in group D

tween histologic structure and prognosis (table 3) The decreasing success of treatment with higher grades of malignancy is due mainly to

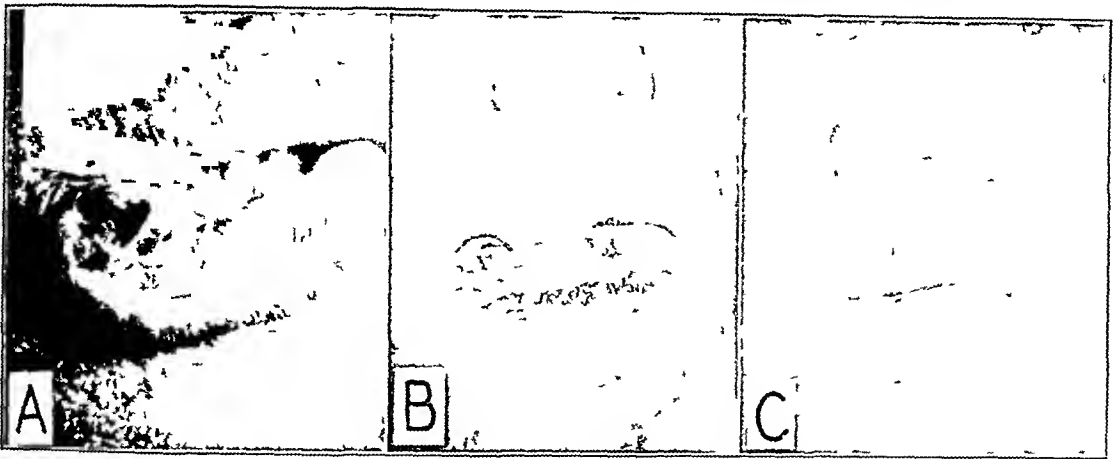


Fig 6—Example of primary lesion of group C (average diameter, 2 to 3 cm) 4 squamous cell carcinoma, B, granulations after removal of final layer of fixed tissue C, healed lesion Metastatic submaxillary nodes on the right side were partially resected surgically and then radically removed by the chemosurgical technique The patient remains free of cancer after five years

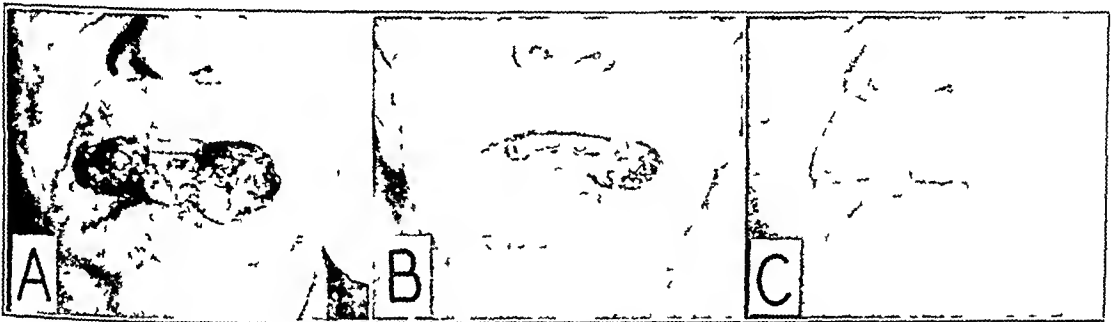


Fig 7—Example of primary lesions of group D (average diameter, 3 cm or more) 4 squamous cell carcinoma, B, granulations after removal of final layer of fixed tissue C, healed lesion The patient refused neck dissection, so he was referred for palliative roentgen therapy The lip was free of cancer when last seen ten months after treatment



Fig 8—Example of primary lesion of group C at the commissure 4 squamous cell carcinoma involving mostly the upper lip but also the lower lip and the buccal mucosa at the corner of the mouth B granulations after removal of the final layer of fixed tissue, C, healed lesion The patient remains free of cancer after eighteen months

Effect of Histologic Grade of Malignancy on Prognosis—Classification of the 168 cancers of the lip on the basis of Broder's four grades of malignancy revealed a marked correlation be-

the greater tendency of the undifferentiated cells to metastasize Of the 4 primary lesions which could not be eradicated 2 were of grade 2 1 of grade 3 and 1 of grade 4

Effect of Previous Treatment on Prognosis—In the 168 cases in the determinate group in which cancers of the lip were treated chemosurgically, 41 (24.4 per cent) of the patients had been unsuccessfully treated by surgical operation, roentgen rays, radium or caustics, alone or in combination, before reporting to the chemo-

TABLE 1—End Results After Six Months or More in 176 Cases of Cancer of the Lower Lip

This series includes the cases of all patients with histologically proved squamous cell carcinomas, both early and advanced previously untreated and recurrent, with and without metastasis who were admitted to the chemosurgery clinic from July 7, 1936 to May 29, 1943.

Total number of cases	176
Indeterminate group	
Patients dead from other causes without recurrence	1
Patients lost from observation without recurrence	7
Total number	8
Determinate group	
Total number	168
Unsuccessful results	
Patients dead as a result of cancer	9
Patients lost from observation with cancer	3
Patients living with cancer	2
Total number	14
Successful results	
Patients free from cancer after six months or more	154
Six month end results	
Total number of cases with successful results divided by total number of determinate cases (154 ÷ 168)	91.7%

TABLE 2—Effect of Size of Primary Lesion on Prognosis

Group	Average Diameter Cm	Number of Lesions	Successful Results	
			Number	Per Cent
A	Under 1	33	32	97.0
B	1-2	86	85	98.8
C	2-3	33	30	90.9
D	3 or more	16	7	43.8
All groups		168	154	91.7

TABLE 3—Effect of Histologic Grade of Malignancy on Prognosis

Grade	Number of Lesions	Successful Results	
		Number	Per Cent
1	44	44	100.0
2	104	97	93.3
3	16	12	75.0
4	4	1	25.0

TABLE 4—Effect of Previous Unsuccessful Treatment on Prognosis

	Number of Patients	Successful Results	
		Number	Per Cent
Previously untreated	127	121	95.3
Previously treated	41	33	80.5

surgery clinic. While it was possible to salvage 33 (80.5 per cent) of these cases by the chemosurgical treatment, the cure rate was appreciably below the 95.3 per cent for the cases in which the patients had not been treated previously (table 4).

The unfavorable effect of previous treatment is probably largely due to delay in eradication of the cancer of the lip, with a resulting increase in extent of the primary lesion and incidence of metastasis.

Effect of Metastasis Diagnosed at Onset of Treatment on Prognosis—The most important factor in determining prognosis is the presence or absence of metastasis. Thus of the 15 cases in which submental, submaxillary or cervical metastases were diagnosed at the onset of chemosurgical treatment, only 4 (26.7 per cent) had

TABLE 5—Effect of Metastasis Diagnosed at Onset of Treatment on Prognosis

Metastasis Diagnosed at Onset of Treatment	Successful Results		
	Number	Number	Per Cent
Absent	153	150	98.0
Present	15	4	26.7

TABLE 6—Three Year and Five Year End Results of Cases of Cancer of the Lower Lip

This series includes the cases of all patients with histologically proved squamous cell carcinomas, both early and advanced previously untreated and recurrent with and without metastasis, who were admitted to the chemosurgery clinic from July 7, 1936 to Oct. 28, 1940 for the three year group and from July 7, 1936 to Nov. 19, 1938 for the five year group.

	Three Year Period	Five Year Period
Total number of cases	91	40
Indeterminate group		
Patients dead from other causes without recurrence	13	8
Patients lost from observation without recurrence	5	5
Total number	18	13
Determinate group		
Total number	73	32
Unsuccessful results		
Patients dead as a result of cancer	5	3
Patients lost from observation with cancer	2	1
Patients living with cancer	1	0
Total number	8	4
Successful results		
Patients free from cancer for three years or more (first column) or for five years or more (last column)	65	28
Three year end results		
Total number of cases with successful results divided by the total number of determinate cases (65 ÷ 73)	89%	
Five year end results		
Total number of cases with successful results divided by the total number of determinate cases (28 ÷ 32)		87.5%

a successful outcome, while of the 153 cases in which metastases were not found at that time successful results were obtained in 98 per cent (table 5).

Three Year and Five Year End Results—Every effort is made to trace all patients for at least five years. There are, of course, the inevitable deaths from intercurrent disease and the patients lost from observation before the end of the three year or five year period. These patients' cases are included in the indeterminate group, after the example of Martin, MacComb

and Blady. The determinate group, on the other hand, includes those cases in which patients have died from cancer, been lost from observation with cancer or are living with cancer and those free from cancer after the three year or five year periods.

In the three year period successful results were obtained in 89 per cent of the 73 cases in the determinate group (table 6) and in the five year period, in 87.5 per cent of the 32 cases in this group (table 6).

THERAPEUTIC RESULTS IN CASES OF CANCER OF THE UPPER LIP

Eight patients with the relatively uncommon cancer of the upper lip (fig 9) were treated in the chemosurgery clinic. A number of commissural lesions involved the upper lip to some extent (fig 8), but reports of these are omitted.



Fig 9—Squamous cell carcinoma of the upper lip. A, before, and B, after, chemosurgical treatment. The patient remains free of cancer after fifteen months.

here because they were included in the preceding series. There were 2 patients with unsuccessful results, 1 for whom chemosurgical treatment was temporarily stopped until another necessary operation could be performed, and who suddenly died of coronary occlusion before chemosurgical treatment could be resumed, 1 in whom cervical metastases developed which at the time of writing have recurred after two surgical dissections, although the upper lip remains free of cancer.

The end results after six months or more were successful for 5 of the 7 cases (71.4 per cent) in the determinate group. At the five year period results were successful for 2 of the 4 cases in the determinate group.

CHEMOSURGICAL TREATMENT OF INOPERABLE SUBMAXILLARY NODES

As previously mentioned, patients with regional metastases are referred for standard surgical

dissections except for those with large submaxillary masses firmly adherent to the mandible and other structures (fig 10). These fixed masses are removed chemosurgically if the grade of malignancy is not too great and if there are no inoperable lesions in the cervical chain.

The technic is essentially the same as that for the lesions on the lip, chemical fixation being carried to a microscopically cancer-free level. This procedure usually exposes at least the mandible, the submaxillary salivary gland and the mylohyoid and sternocleidomastoid muscles (fig 10 B). The mandibular branch of the facial nerve is often interrupted. The cancer almost invariably involves the periosteum of the mandible, and in some cases the bone is eroded. The extent of involvement of bone can be seen grossly, which is fortunate because it is of course impossible to make frozen sections of bone. However, speci-

mens of soft tissue eroding the bone can be sectioned for confirmation of gross visualization. The zinc chloride fixative penetrates well through the bone, though somewhat more slowly than through soft tissues. The fixed bone is removed with a rongeur or a chisel. The process is repeated until solid, uninvolved osseous tissue is reached.

After three or four weeks a line of demarcation forms under the remaining layer of fixed bone, and the sequestrum can then be grasped with a rongeur and lifted off the sound bone. The granulation tissue thus exposed supports the rapid growth of the skin across the wound. The resulting scar is not too disfiguring (fig 10 C).

A total of 12 patients with inoperable submaxillary nodes were treated chemosurgically. The primary lesions had been removed by surgical operation and/or irradiation in all but 3 patients, who had been treated chemosurgically.

Five of the metastases were widespread, cauliflower-like masses, which were obviously hopeless but which were removed to relieve the patients temporarily of the large, malodorous lesions. Of the 7 remaining patients 1 was apparently free of cancer for one year (the patient died three years later of undetermined cause) and another appears to be free of cancer at the time of writing, after two years. In the other 5 either the metastatic nodes proved to be too far advanced for complete removal or else cervical metastases were uncontrolled.

THERAPEUTIC RESULTS FOR OTHER NEOPLASMS OF THE LIP

The microscopic control of excision afforded by the chemosurgical method is also of value in assuring the complete removal of other neoplasms.

Squamous Cell Papilloma—Four papillated, hyperkeratotic lesions were removed from the lower lip by chemosurgical measures, with no return of the papillomas after periods of from seven months to four years.

Fibroma—One fibroma of the lower lip was removed chemosurgically, and there was no evidence of it when the patient died of other causes after three months.

Epidermoid Cyst—One post-traumatic epidermoid cyst was chemosurgically excised from the lower lip, with no return after seven months.

THERAPEUTIC RESULTS FOR PRECANCEROUS LESIONS OF THE LIP

In the prevention of cancer of the lip, the chemosurgical technic is of value as a simple and a reliable method for the eradication of precancerous lesions. The accurate histologic diag-



Fig 10—A, fixed submaxillary nodes secondary to a squamous cell carcinoma of the lower lip (the latter had been treated with radon seeds over a period of two years, after which a surgical resection and two plastic operations were done), B, after chemosurgical treatment, showing exposed mandible, mylohyoid muscle and sternocleidomastoid muscle, C, healed lesion. The patient showed no evidence of cancer when last seen one year later, he died of undetermined cause after three years.

Basal Cell Carcinoma—Most basal cell carcinomas involving the lip do so by invasion from an origin in the skin outside of the lip proper but reports on these are omitted from this paper. Only one basal cell carcinoma originating in the lip was treated chemosurgically. It was a lesion 1.4 cm in diameter on the lower lip. The patient was free of cancer after five years.

Hemangioma—Half of the hemangiomas in this series were not diagnosed as such until the sections were examined because when these lesions become ulcerated, hemorrhagic and crusted they often resemble cancer. All of the 8 hemangiomas treated chemosurgically were of the capillary type and all involved the lower lip. None of them showed any evidence of recurring after from three months to five years.

nosis afforded by the method is a distinct advantage, because it is often impossible to be sure clinically whether these lesions are precancerous or cancerous.

The technic is essentially the same as that used in the treatment of cancer. Horizontal sections through the under surface of the first excised specimen are made to make sure there are no deeper downgrowths and then the specimen is turned on edge, and vertical sections are made for diagnosis.

Precancerous Keratoses, Ulcers and Fissures—These precancerous lesions are considered together because they grade into each other and seem to be simply different manifestations of the same process. The initial lesion is usually a keratosis—often starting as a localized scaly

or horny excrescence at one point in a narrow hyperkeratotic line extending across the entire lip. The adherent scale may be picked off by the patient or otherwise traumatized, forming an ulcer, which may heal temporarily but which more often persists and extends. In patients with clefts along the lower lip or at the commissures the ulcers may take the form of non-healing fissures. Occasionally the granulations are so prominent that a diagnosis of granuloma pyogenicum is justified.

For a total of 44 patients these precancerous lesions of the lip were removed chemosurgically. Of these patients, 34 were followed for periods of from one month to seven years (average, two years). At the time of writing none of the lesions had recurred nor had the remaining tis-

Radiation Ulcers—The nonhealing ulcers which may result from roentgen or radium treatment of lesions of the lip may be classed as precancerous lesions. The purpose of the chemosurgical treatment of these lesions is to remove the poorly vascularized, scarred tissue so that prompt healing occurs.

Six radiation ulcers were treated chemosurgically and of these 5 were followed from one month to seven years (average, thirteen months). Only 1 broke down after treatment, but further chemosurgical therapy healed it. None underwent malignant change.

COMMENTS

As previously stated, the microscopic control provided by the chemosurgical method is respon-

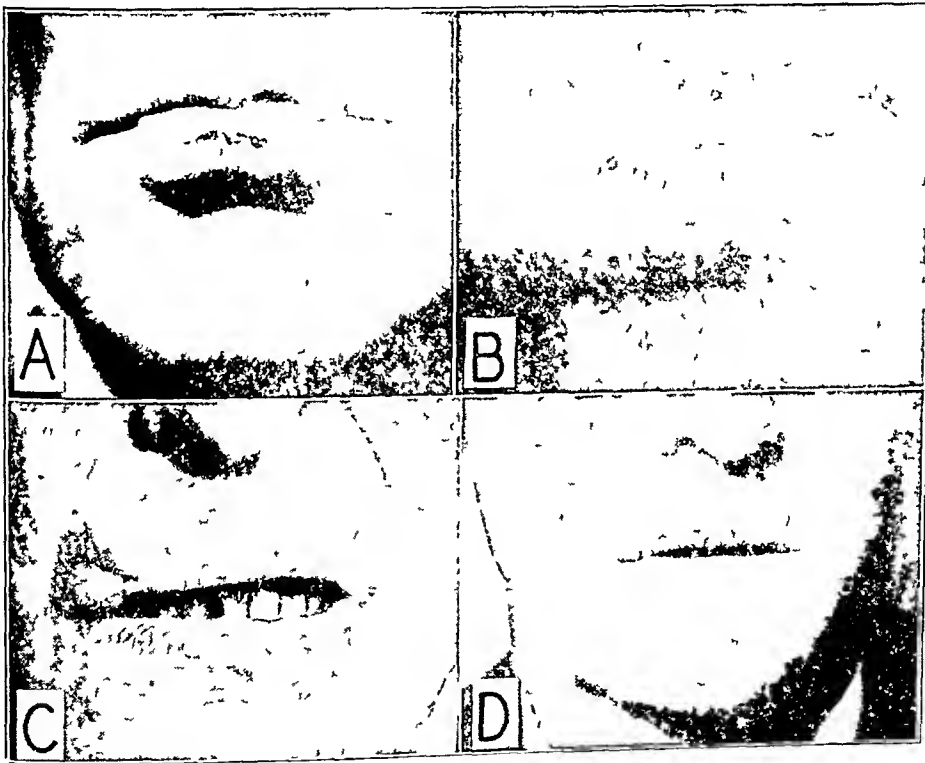


Fig 11—Precancerous lesions. A, keratosis with ulceration and crusting, B, healed lesion two months after chemosurgical removal, C, leukoplakia, D, healed lesion thirteen months after chemosurgical removal.

sue undergone malignant change. In none of the patients was there a defect in the lip, and the scars were practically invisible (fig 11 A, B).

Leukoplakia—Because leukoplakia presents a definite clinical and histologic entity (fig 11 C, D) it is considered separately from the other precancerous lesions, though the hyperplasia and the hyperkeratosis in all of these conditions are probably essentially similar.

Sixteen patients with leukoplakia were treated chemosurgically. Ten were followed for periods of two months to six years (average two years) and not a single instance of recurrence or malignant change was observed.

sible for two important advantages in the treatment of cancer of the lip, namely (1) unprecedented reliability and (2) conservatism.

The great reliability of the method is attested by the fact that in 197 cases of cancer of the lower lip there were only 4 failures to eradicate the primary lesion and as previously pointed out none of these failures could be attributed to any fault of the method. This record was obtained despite the fact that 244 of the primary lesions had earlier been unsuccessfully treated by other methods.

Moreover the cure rate of 87.5% over the five year period compares favorably

that at the large, well known centers for the treatment of cancer in this and other countries. Thus the end results after five years given in recent years by workers from some of these institutions are as follows: Martin and associates³ (1941), 70 per cent, Bergendal⁴ (1938), 80 per cent, Schreiner and Christy⁵ (1942), 75.7 per cent, Newell⁶ (1939), 61.6 per cent, and Lacassagne⁷ (1929), 58 per cent.

The conservatism of the method and the consequent cosmetic results are shown in the preceding photographs. Defects requiring subsequent plastic repair are obtained only when advanced lesions are removed. When defects result they usually are so minimal that most of the patients refuse the simple repair offered them.

The importance of the microscopic control afforded by the chemosurgical method was repeatedly brought home when, time after time, unsuspected outgrowths of small caliber from the main tumor mass were found microscopically, at times extending a considerable distance after becoming grossly invisible. In several instances the cancer extended along nerves picked up in the chin and followed them through the mental foramen and then for several centimeters along the inferior dental canal. A reconstruction of

cancer with such a tendency to follow nerves and the appearance of a pincushion on its under surface. More often, however, the slender outgrowths did not follow any specific structure but simply followed along planes of reduced resistance to their spread. Often the orbicularis oris muscle had slightly more resistance to the cancer than the softer tissues anterior and posterior to it, and the chemosurgical method allowed the preservation of a maximum amount of this structure.

The chemosurgical procedure carried practically no risk, even in elderly patients with advanced cancer of the lip. In no case was infection a problem, even though many of the patients had severe oral sepsis, the absence of infection was due to the sterilization of the lesion

by the fixative during the treatment and to the resistance to germs of the granulation tissue after the separation of the final layer of fixed tissue. In fact, after chemosurgical treatment the dressings can safely be cared for by the patient himself. Hemorrhage during separation of the final layer of fixed tissue occurred in 3 patients of this series. Two hemorrhages were stopped within twenty minutes by the application of pressure and one was stopped by a suture-ligature.

The low incidence of metastasis appearing after chemosurgical removal of the primary lesion confirms our earlier impression¹ that chemical treatment of cancers has not the slightest tendency to cause further metastasis. Whether or not this method has less tendency to produce metastasis than surgical operation, with its handling factor, or irradiation, with its delay factor, cannot be determined with the statistics now at hand.

Chemosurgical treatment is particularly advantageous for cancer of the lip recurrent after surgical operation or irradiation. Such lesions often respond poorly to repetition of the original therapy, but they almost invariably respond to chemosurgical treatment.

This technic requires specialized training and a specially equipped clinic. It is my opinion that one such clinic should eventually be made available to every large center of population.

SUMMARY AND CONCLUSIONS

The chemosurgical treatment of cancer of the lip has the great advantage of microscopic control of excision. This feature accounts for the unprecedented reliability and the conservatism of the method.

The reliability of the method is indicated by the unusually high proportion of successful results after six months (91.5 per cent of 164 cases), after three years (89 per cent of 73 cases) and after five years (87.5 per cent of 32 cases). Although 24.6 per cent of the cancers of the lip had previously been unsuccessfully treated by other methods, 97.7 per cent of the primary lesions were eradicated by chemosurgical treatment.

The conservatism of the method allows preservation of a maximum amount of uninvolved lip tissue, with consequent excellent cosmetic results.

It is also an efficient treatment for carcinoma of the upper lip, for basal cell carcinoma, for various benign neoplasms and for precancerous lesions of the lip.

Firmly fixed submaxillary nodes constitute the only metastatic lesions for which chemosurgical treatment is indicated.

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4 Bergendal, A. A Review of Twenty Years' Radium Treatment of Lip Cancer at the Radiological Clinic, Lund, Sweden, *Acta radiol* **19** 103 (May) 1938.

5 Schreiner, B. F., and Christy, C. J. Results of Irradiation Treatment of Cancer of the Lip. Analysis of 636 Cases from 1926-1936, *Radiology* **39** 293 (Sept) 1942.

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EFFECTS OF CONTINUOUS AND OF INTERMITTENT APPLICATION OF A TOURNIQUET TO A TRAUMATIZED EXTREMITY

ALFRED BLALOCK, M D

BALTIMORE

It is generally recognized¹ that one should not employ a tourniquet for the control of bleeding if other means will suffice. If the use of a tourniquet is necessary, it is desirable to release it from time to time in order that some oxygen may be transported to the ischemic tissues. Unfortunately, the conditions in which the use of a tourniquet is required for the control of bleeding are usually such that intermittent release results in the loss of a prohibitive quantity of blood. Nevertheless it appeared to be of interest to investigate experimentally the comparative effects of continuous and of intermittent application of a tourniquet to a traumatized extremity. In previous experiments² it was found that the application of a tourniquet to a traumatized extremity reduced the chances of survival of the animal. Additional studies³ showed that cooling of the part distal to the

tourniquet lessened the ill effects of the ischemia and the anemia.

Large animals were used in all studies. Anesthesia was induced by the intravenous administration of 30 mg of pentobarbital sodium per kilogram of body weight. Additional injections of 5 mg per kilogram were given as needed. Two experiments were performed simultaneously, in one the application of the tourniquet was continuous, and in the other it was intermittent. One of the posterior extremities was struck approximately four hundred and fifty moderately severe blows with a padded hammer. Immediately thereafter a tourniquet of heavy rubber tubing was applied tightly around the upper part of the thigh. In half of the experiments the tourniquet was left in place for five hours. The results of these experiments are given in table 1. In the other experiments the tourniquet was released for two minutes out of every thirty minutes during the five hour period. The results of these experiments are given in table 2.

The differences in the two groups of experiments were more marked than had been anticipated. Only 1 of the 13 animals survived in the group in which the tourniquet was left in place for five hours whereas 8 of the 13 survived in the group in which the tourniquet was released intermittently. Other differences in the two groups are listed in table 3. These results simply confirm prevailing impressions in regard to the dangers associated with the prolonged use of a tourniquet on an injured extremity.

From the Department of Surgery of The Johns Hopkins University and Hospital. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Offices of Scientific Research and Development and Johns Hopkins University.

1 Wilson, H, and Roome, N W. The Effects of Constriction and Release of an Extremity. An Experimental Study of the Tourniquet, *Arch Surg* **32** 334 (Feb) 1936.

2 Duncan, G W, and Blalock, A. The Effects of the Application of a Tourniquet on the General Response to Gross Trauma to an Extremity, *Surgery* **13** 401 (March) 1943.

3 Blalock, A. Effects of Lowering Temperature of an Injured Extremity to Which a Tourniquet Has Been Applied, *Arch Surg* **46** 167 (Feb) 1943.

TABLE 1—Continuous Application of Tourniquet to a Traumatized Extremity

Experiment No	Body Weight, Kg	Arterial Pressure, Mm Hg					Hematoerit Reading					Urine			Hours Lived After Tourniquet Off	Loss of Fluid, % of Body Weight
		Con trol	5 Hr	7 Hr	9 Hr	11 Hr	Con trol	5 Hr	7 Hr	9 Hr	11 Hr	5 Hr	5-9 Hr	Casts		
6	10.8	153	173	68	52		46.6	44.9	63.5	62.9		16	5	0	5	5.23
8	12.1	128	138	65			43.9	48.6	66.2	66.1		20	2	+	4	4.95
10	12.7	128	153	118	103	103	37.8	34.8	54.2	52.8		13	12	0	Recovered	
12	9.5	133	118	110	90	48	38.8	39.2	45.1	44.4	42.0	23	16	+++	8	4.47
14	10.3	118	173	93			45.7	56.7	72.2			13	6	0	2	4.37
16	13.4	128	150	98	70	65	49.0	53.4	67.8	66.7	64.5	25	25	+++	13	5.71
18	15.4	153	153	70	30		52.4	52.4	67.4	69.7		30	2	0	4	3.73
20	12.1	118	150	98			46.7	40.3	54.7			31	5	+++	4	6.81
22	9.7	112	152	40			34.7	35.3	42.7			29	2	0	3	4.64
24	10.0	118	182	98	78	60	41.0	46.0	62.1	60.7	61.2	27	15	+++	9	4.59
26	9.2	128	152	75	45	40	45.7	47.2	52.9	52.6	51.4	25	12	++	7.5	4.89
28	13.6	130	148	72			43.8	45.0	60.9	69.8		21	3	+	4	6.05
				6 Hr					6½ Hr							
30	10.4	143	153	65			41.9	43.8	56.5			50	10	+	1.5	4.03

TABLE 2—Intermittent Application of Tourniquet to a Traumatized Extremity

Experiment No	Body Weight, Kg	Arterial Pressure, Mm Hg					Hematoerit Reading					Urine			Hours Lived After Tourniquet Off	Loss of Fluid, % of Body Weight
		Con trol	5 Hr	7 Hr	9 Hr	11 Hr	Con trol	5 Hr	7 Hr	9 Hr	11 Hr	5 Hr	5-9 Hr	Casts		
5	11.8	128	138	118	88	6.	36.5	51.0	57.8	60.3	62.7	39	15	+++	9	4.02
7	12.0	123	163	113	90	88	42.9	52.4	57.7	56.8	58.6	15	15	0	Recovered	
9	11.1	118	78	4.			40.6	46.8	47.0	45.0		17	6	+	4	3.82
11	9.4	118	133	80	68	60	38.0	43.2	47.3	46.4	45.4	26	6+	+++	9	3.99
13	11.5	143	108	100	90	70	49.7	59.4	62.0	69.4	60.7	5	8	0	Recovered	
15	11.4	118	158	133	120	112	40.0	51.8	52.8	53.1	53.2	39	31	0	Recovered	
17	15.3	110	160	103	93	88	36.2	44.1	46.3	45.7	46.5	22	12	++	Recovered	
19	11.8	112	148	128	98	93	40.3	44.0	46.8	43.5	46.0	25	36	0	Recovered	
21	9.4	105	133	72	62	42	37.4	42.9	45.1	45.3	45.1	22	4	+	7	6.13
23	10.5	133	170	102	123	128	50.8	51.7	59.8	61.2	63.1	39	27	0	Recovered	
25	10.7	138	148	128	98	92	44.6	47.3	53.3	52.2	51.0	21	44	0	Recovered	
27	15.4	118	162	142	138	128	50.8	38.4	45.8	47.5	45.6	42	36	0	Recovered	
29	8.8	170	133	98	83	63	53.0	55.2	59.6	57.9	58.6	20	7	+++	38	5.12

TABLE 3—Comparison of Effects of Continuous and of Intermittent Application of Tourniquets to Traumatized Extremities

Observations	Continuous Application of Tourniquet (13 Experiments)	Intermittent Application of Tourniquet (13 Experiments)
Swelling of leg at end of 5 hour period	Very little	Marked
Extent of swelling several hours after release	Extensive, involving foot, ankle and groin	Limited in main to injured area
Color of skin after release	Blue	Beefy red
Knee reflexes after release	Absent	Present
Quantity of anesthetic agent	Less required	More required
Average increase of hematoerit reading at time of release (5 hour period)	1.5	6.2
Average increase of hematoerit reading 2 hours later (compared with control)	10.6	9.9
Output of urine after release of tourniquet	Very small amount	Moderate amount
Casts in urine	Moderate number	Very few
Average blood pressure (mm Hg) just before end of 5 hour period	154	140
Average blood pressure 2 hours later	77	104
Number of animals surviving	1	8
Average period of survival of remainder	5+ hours	13+ hours
Regional loss of fluid per cent of body weight	4.97 (12 experiments)	4.61 (5 experiments)

EFFECT OF HYPOPROTEINEMIA ON SUSCEPTIBILITY TO SHOCK RESULTING FROM HEMORRHAGE

COLONEL I S RAVDIN CAPTAIN H G McNAMEE AND
LIEUTENANT J H KAMHOLZ

MEDICAL CORPS, ARMY OF THE UNITED STATES

AND
J E RHOADS, M D

PHILADELPHIA

A positive relationship between hypoproteinemia and susceptibility to shock has been predicated on the observation that the hypoproteinemic animal is prone to have a decreased plasma volume¹ and that it is generally incapable of replacing any further loss in plasma protein rapidly because the stores of labile protein are largely exhausted. Little if any direct experimental evidence on this point has been reported, and yet the importance of this relationship is so practical, from the standpoint of both war surgery and civilian surgery, that the following experiments were undertaken with a view to establishing not only whether such a relationship does exist but whether it is quantitatively of sufficient importance to justify greater care in avoiding hypoproteinemia in persons who are likely to be exposed to shock-producing injuries.

METHOD

The experiments were carried out on mongrel dogs weighing 8 to 13 Kg. Hypoproteinemia was produced by repeated plasmaphereses in animals maintained on the following diet, which appeared to be adequate in all respects but protein. The amount offered was approximately 90 calories per kilogram per day to each dog, and in no instance did the animals eat all the food.

Diet			
	Per Cent by Weight	Calories	Per Cent of Total Calories
acrose	55.1	220	44.7
extrose	18.17	73	14.7
ard	23.19	200	40.6
one nsh	2.36		
it mixture	1.18		
Total	100.0	493	100.0
lus cod liver oil	1.5		

The following supplements (made up in an aqueous solution of about pH 5) were fed separately from the preceding diet: 0.1 mg of thiamine hydrochloride per kilogram per day, 400 mg of Wilson's liver fraction per kilogram per day, and 50 mg of choline chloride per kilogram per day. Each animal was given approxi-

mately 5 cc daily. If most of the ration was consumed regularly they were mixed with the food, otherwise, when the intake of food was erratic, the supplements were given separately to insure their consumption.

The method of producing shock was similar to that used by Govier and Greer.³ Successive amounts of blood were withdrawn from a femoral artery at fifteen minute intervals until the blood pressure remained below 60 mm of mercury for thirty minutes. Measurements of the blood pressure were made in the femoral artery. In some instances continuous recordings were made with a kymograph. In other experiments the arterial pressure was measured against a column of mercury at the required intervals.

Experiments were completed with 5 normal animals and 6 hypoproteinemic animals. Four of the hypoproteinemic animals were allowed to recover for periods of one to seven months, at which time the serum protein concentration had in each instance returned to normal range for the species. The procedure for causing shock was carried out again on these animals with somewhat irregular results.

Loss of Blood Resulting in Depression of Blood Pressure to Below 60 Mm of Mercury for Thirty Minutes

Normal Animals			Hypoproteinemic Animals			Hypoproteinemic Animals After Restoration of Serum Protein Level		
Dog No	Serum Protein Gm / 100 Ml	Loss of Blood Ml / Kg	Dog No	Serum Protein Gm / 100 Ml	Loss of Blood Ml / Kg	Dog No	Serum Protein Gm / 100 Ml	Loss of Blood Ml / Kg
127	6.1	51.9	102	4.1	25.6	102	6.4	2.7
475	5.3	48.1	41	3.0	25.2	41	6.8	2.5
493	6.2	37.9	182	3.7	25.7	182	7.2	4.4
646	5.5	45.1	207	1.5	27.9	207	7.6	2.2
729	5.9	48.0	796	2.9	27.8			
			777	3.8	27.7			

COMMENT

In experimental plasmaphereses in our laboratory it has been usual to bleed the animal to the first sign of air hunger and then to stop. It has been our observation that if the bleeding is continued much beyond this point the animal dies. As the procedure is repeated the amount of blood which may be drawn decreases progressively so that as the serum protein con-

3 Govier W M and Greer C M J Surg Res & Exper Therap 72 317 (1951)

From the Harrison Department of Surgical Research School of Medicine, University of Pennsylvania
1 Whipple, G H Am J M Sc 196 609 1938
2 Liver Fraction E, Wilson Laboratories Chicago

tration approaches the edema level the amount of bleeding necessary to produce air hunger is about half the amount necessary when the first plasmapheresis is done

Likewise, in clinical work it is often observed that patients who have to undergo a number of successive operative procedures react favorably at first and poorly later. This is particularly true of patients who have prolonged suppuration or prolonged drainage from a high intestinal fistula

The well nourished, well developed, well rested person has always been recognized as a superior surgical subject. The precise factors which produce this superiority have never been clearly defined. It is probable that they are numerous, and it is also likely that the nutritional factors are important. We believe that for surgical patients protein nutrition is of especial importance. To what degree the presence of ample stores of protein conditions the body to withstand the hazards of surgical operation is impossible to state.

Earlier studies from this laboratory have demonstrated that hypoproteinemia interferes with healing of wounds,⁴ and with gastric emptying,⁵ retards intestinal motility^{5a} and delays the calcification of callus in dogs following experimental fracture.⁶ There is some evidence that it plays an important role in resistance to infection.⁷

4 Thompson, W. D., Ravdin, I. S., and Frank, I. L. Effect of Hypoproteinemia on Wound Disruption, *Arch Surg* **36** 500 (March) 1938. Thompson, W. D., Ravdin, I. S., Rhoads, J. E., and Frank, I. L. Use of Lyophilic Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption, *ibid* **36** 509 (March) 1938.

5 (a) Mecray, P. M., Barden, R. P., and Ravdin, I. S. *Surgery* **1** 56, 1937. (b) Barden, R. P., Ravdin, I. S., and Frazier, W. D. *Am J Roentgenol* **38** 196, 1932.

6 Rhoads, J. E., and Kasinskas, W. *Surgery* **11** 38, 1942.

7 Robertson, E. C., and Tisdall, F. F. *Canad M A J* **40** 282, 1939. Cannon, P. R. *J Immunol* **44** 107, 1942.

The present experiments indicate that hypoproteinemia of the degree produced increased susceptibility to hemorrhagic shock about 67 per cent. That is, the mean loss of blood necessary to produce a standard effect on the circulation in normal animals was 67 per cent greater than the mean loss of blood required to produce the same effect in the hypoproteinemic animals. Furthermore, the figures were rather consistent, the weakest normal animal withstood 5 cc per kilogram more loss of blood than the strongest hypoproteinemic animal.

The animals whose protein had been restored on the other hand, varied considerably in their responses. Dogs 152 and 41 went into shock as easily as they had when they were hypoproteinemic, even though the serum protein concentration had returned to normal. The other animals, however, showed considerable improvement in their resistance to loss of blood. In dog 796 a much longer interval elapsed (seven months) but for each of the other 3 animals the interval for recovery was about two months.

It should also be noted that some of the normal animals had serum protein concentrations a little below normal and yet withstood hemorrhage very well. All of these animals, however, had concentrations which were well above the level for edema for the dog.

These irregularities suggest that plasma protein levels near the normal range cannot be relied on to indicate the ability of the animal to withstand hemorrhage but that when severe hypoproteinemia is present it is probable that susceptibility to hemorrhagic shock is considerably increased.

CONCLUSIONS

Chronic hypoproteinemia caused a distinct increase in the susceptibility of dogs to shock due to hemorrhage.

Two of the dogs which had been hypoproteinemic appeared to remain hypersensitive to hemorrhage even after their serum protein had returned to a normal level.

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